VOLUME XXVI NUMBER 2

DISEASES

of the

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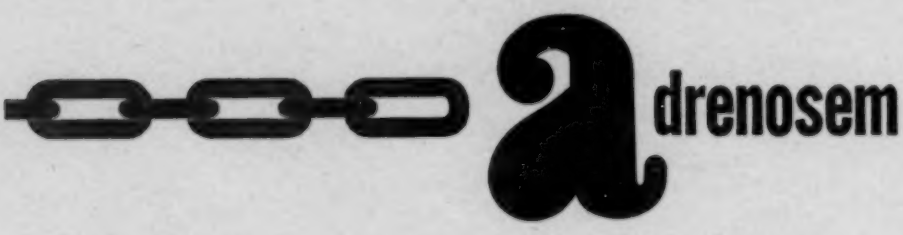
*Sherber, D. A.: The Control of Bleeding. Am. J. Surg. *46*:331 (Sept.) 1963.



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1. Hobby, G. L., Lenert, T. F., Rivoire, Z. C., Donikian, M., and Pikula, D.: Am. Rev. Tuberc. 67:808, 1953.

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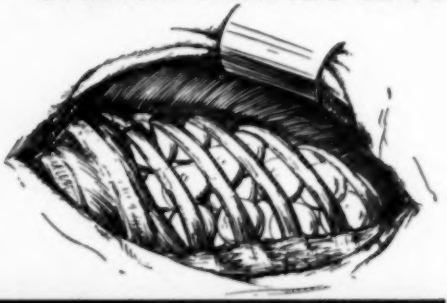

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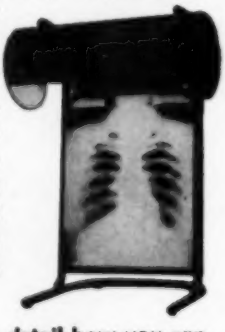

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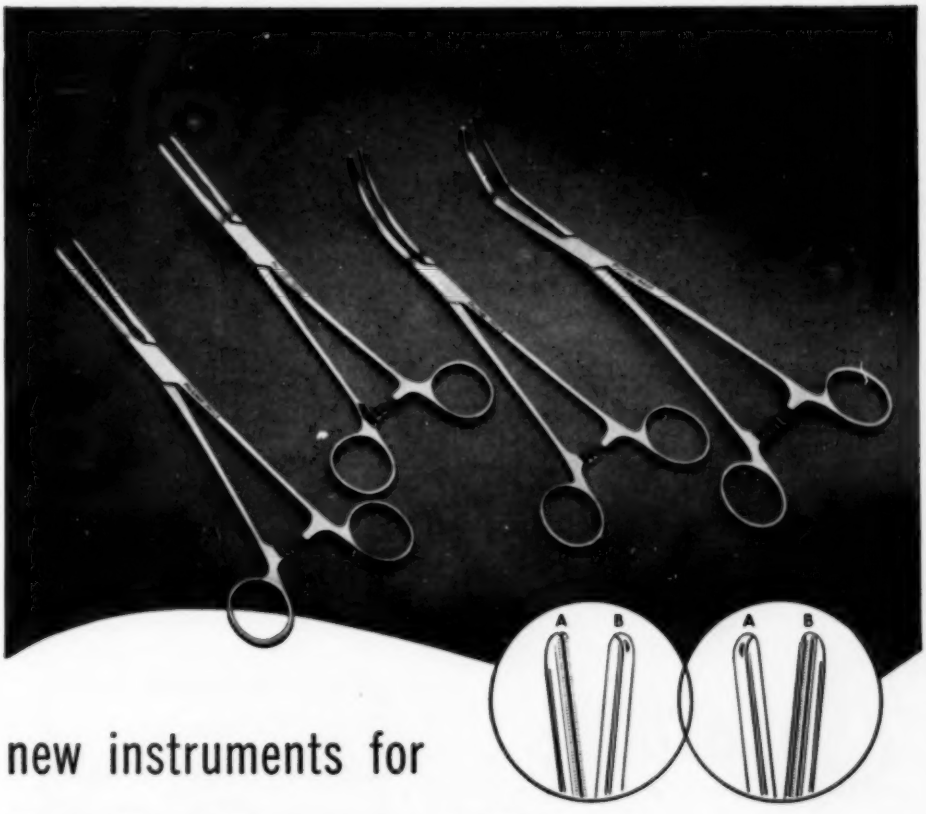

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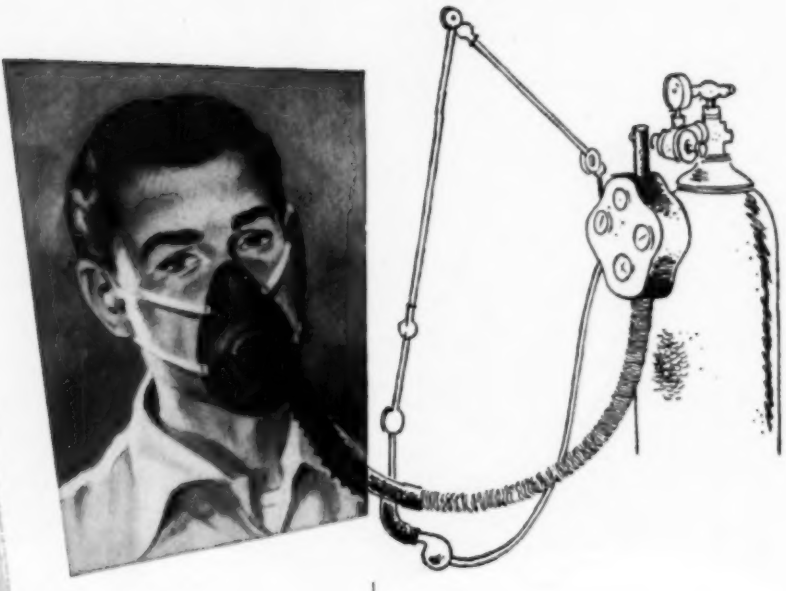

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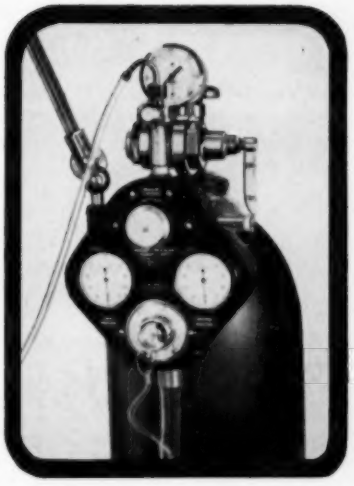

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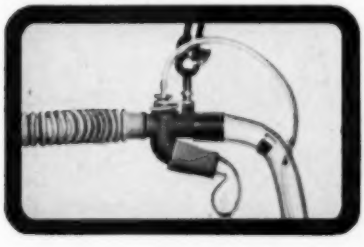

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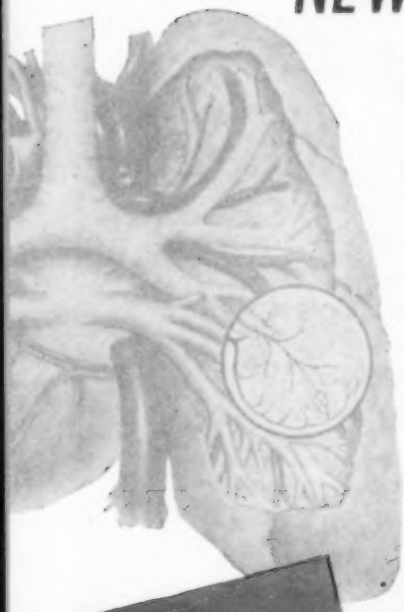

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DISEASES *of the* CHEST

VOLUME XXVI AUGUST 1954 NUMBER 2

The Role of Segmental Resection for Bronchiectasis in Conserving Pulmonary Function

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One of the fundamental principles of surgery is the removal of diseased tissue with all possible preservation of healthy tissue. In thoracic surgery, fulfillment of this principle was not always possible while the pulmonary lobe was the smallest unit of excision. The concept of the pulmonary segment as a unit of excision, and the consequent development of requisite surgical techniques, now extend the scope of safe surgical therapy to cases which heretofore presented contraindicating hazards.

The pulmonary architecture is so well designed that seldom are *all* the segments of any lung involved. Disease before puberty may damage a considerable portion of a lung, but the remaining healthy tissue will so hypertrophy that it can fulfill its physiological requirements, and become important to save. On the other hand, when pulmonary disease occurs in the adult the remaining healthy tissue may become overtaxed by the stress of constant cough and the influence of intimate toxicity. Although such tissue may resist actual infection, it can, by means of compensatory emphysematous change, steadily decrease in its powers of physiological function.

In either of these situations, the best chance the patient has of release from respiratory distress is excision of the disease. Such surgery should be planned and carried out on a segmental basis, and at the optimum time.

Two cases are reported demonstrating the value of segmental resection in conserving pulmonary function.

Case 1: Mrs. L.R., age 46, had moderately severe pulmonary hemorrhages five times between April 1949, and May 1950. Bronchography revealed bronchiectasis involving the superior segment of the left lower lobe and the lingula of the left upper lobe. May 17, 1950, a segmental resection of the three involved segments

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TABLE I

	L. R., Age 47	*A. D., Age 29*
Presenting symptoms	Several recurrent pulmonary hemorrhages	Purulent sputum and repeated respiratory infections.
Date of surgery	May 17, 1950	November 17, 1951.
Surgery	Lingula of LUL Sup. seg. LLL	LLL Lingula & ant. seg. LUL.
Post-operative complications	None	None.
Remarks		Left temporary phrenic.
Maximum Breathing Capacity:		
Determined 1/m.	66	84
Predicted Per cent	88	67
Walking Vent.—1/m.	13.9	18
WV/MBC	0.21	0.21
Timed Vital Capacity:		
1 second per cent	78	80
2 seconds per cent	92	90
3 seconds per cent	96	95
Air Velocity Index	0.98	0.90
Vent. Equiv. 1/m.	2.8	2.8
Tidal Vol., cc.	806	748
Min. Vol., 1/m.	8.8	10.4
O_2 Uptake, cc./m.	314	369
Vital Cap., cc.	2120	2932
Funct. Resid. Cap., cc.	1329	1914
Resid. Cap., cc.	918	1044
T. Lung. Cap., cc.	3095	3976
RC/TC—Per cent	30	26
Mixing Index—Per cent N_2	1.00	1.20
O_2 Sat. Per cent*	97	95
pHs—37 Degrees C.*	7.25	7.45
pCO_2—mm. Hg.*	48.8	39
Total CO_2—mm./L*	21.3	26.7

*Determined at rest.

was done without difficulty. The postoperative course was uneventful and the patient was discharged from the hospital on the 16th day. Since surgery there has been no recurrence of pulmonary bleeding and she has continued to work without difficulty. Fifteen months after surgery pulmonary function studies were performed and are summarized in Tables I and II.

Discussion: This patient's clinical problem was recurrent pulmonary hemorrhages coming from bronchiectasis in the left upper lobe and the left lower lobe. If the unit of excision had been lobe instead of segment, it would have been necessary to do a left pneumonectomy as treatment for the pulmonary hemorrhages. The segmental surgery in this patient saved five segments of the left lung.

The results of the ventilatory function studies demonstrate that there is slight impairment to air flow. Total lung volume was 3095 cc. and the residual volume relationship to total lung volume 30 per cent; alveolar nitrogen 1.0 per cent. These figures show that there is an increase in the residual capacity consistent with hyperinflation. The mixing index of 1 per cent indicates that there is no impairment to alveolar air mixing. The differential bronchospirometry findings show that the remaining five segments of the left lung contribute 30 per cent of the total oxygen consumption and 42 per cent of the total ventilation. These five segments indeed contribute at least one third of the total pulmonary function. This case demonstrates the functional value of conservation of healthy pulmonary tissue.

Case 2: Mr. A.D., age 29, had a lung abscess and empyema on the left which was treated by open drainage at the age of three years. Following this episode he had chronic cough and raised small amounts of purulent sputum daily. In 1943, while in the service, he had pneumonia and another lung abscess on the left side. Bronchograms in October, 1946, showed bronchiectasis involving the entire left lung with the exception of the posterior-apical segment of the left upper lobe. Between 1949 and 1951, he had blood streaked sputum on two occasions and developed progressive dyspnea.

At exploratory thoracotomy in November 1951, the left lower lobe and the lingula and the anterior segment of the left upper lobes were boggy and contracted. The posterior apical segment of the left upper lobe was several times its normal size. All the diseased tissue was removed leaving only the one segment (posterior-apical) in the left hemithorax. A temporary phrenic crush was done to reduce the volume of the hemithorax. The postoperative course was uneventful and he was discharged on the 13th day. Since surgery he has returned to full time work as a barber and is now free of pulmonary symptoms. In Tables I and II pulmonary function studies were done and are summarized.

TABLE II

	— — *L. R., Age 47* — —		— — *A. D., Age 29* — —	
	Right Lung	Left Lung	Right Lung	Left Lung
Segments remaining	10	5	10	1
O_2 Per cent	70.0	30.0	77.4	22.6
Vent. Per cent	58.1	41.9	72.0	28.0
Vital Capacity Per cent	66.2	33.8	80.0	20.0

Discussion: This patient presented us with the unusual opportunity to study the function of one pulmonary segment. This remaining segment was hypertrophied and larger than a normal segment. The diseased units became contracted during early childhood, permitting the non-involved segment to enlarge and hypertrophy during the period of body growth.

The results of the total pulmonary function as measured by the M.B.C., walking ventilation, and timed vital capacity demonstrate efficient function for the number of remaining pulmonary segments. The intrapulmonary mixing and residual capacity were within normal limits.

The most significant findings were that the remaining segment contributed 22.6 per cent of total oxygen consumption and 28 per cent of total ventilation.

The differential bronchospirometry clearly illustrates the functional relationship between the one hypertrophied segment on the left to the 10 normal segments on the right.

The value of conserving a single pulmonary segment is shown by these findings.

CONCLUSION

Compensatory hyperinflation of lung tissue following segmental resection does not impair intrapulmonary mixing of gases as shown in both case reports. Pulmonary function of the remaining lung tissue following segmental resection for bronchiectasis is of physiological value.

RESUMEN

Tal como se muestra en los dos casos referidos, la sobredistensión compensadora del tejido pulmonar después de la resección segmentaria no perturba la mezcla de gases intrapulmonar. La función pulmonar del tejido restante después de la resección segmentaria por bronquiectasis, es de valor fisiológico.

RESUME

L'hyperexpansion compensatrice du tissu pulmonaire faisant suite à la résection segmentaire n'empêche pas le mélange des gaz intrapulmonaires, comme il est démontré dans les deux observations rapportées. La fonction du tissu pulmonaire restant après une résection segmentaire pour bronchiectasie garde sa valeur physiologique.

Reversibility of Isoniazid Resistance Developed in Mycobacterium Tuberculosis*

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Introduction

It has often been demonstrated that patients treated with isoniazid or its derivative, after a certain time or after a certain quantity of medication, develop resistant strains of mycobacterium tuberculosis. This conception is generally accepted. On the other hand it is a well known fact that many cases in whom streptomycin treatment has failed, and streptomycin resistant strains are present, are markedly benefitted by isoniazid treatment. Clinical, radiological and bacteriological improvement, including sputum conversion, occur. There are numerous publications dealing with the reversion of streptomycin resistance; and it has been proved that in some cases the streptomycin resistant strains disappeared following further treatment. It has also been demonstrated in vitro, that isoniazid resistant strains may revert to isoniazid sensitivity.[3]

In this laboratory investigations have been conducted in an endeavor to find out if reversion of isoniazid resistance occurs in vivo. Those patients on isoniazid whose tubercle bacilli developed a certain degree of resistance were watched for several months to find out if any change in the degree of resistance occurred.

Method

For testing the resistance sputum, sinus discharge or gastric contents were treated as follows. After elimination of the contaminants, using 3.46 per cent sulphuric acid for 35 minutes, an attempt was made to cultivate the organisms on media containing isoniazid in various concentrations, ranging from 0.02 microgram of isoniazid per cc. to 200 mcgm. per cc. At the beginning Youman's fluid medium was used, and later Loewenstein's egg medium. Every patient's sputum or sinus discharge or gastric content was examined six weekly, monthly, or if found necessary, even at shorter intervals. Every growth on the culture medium was tested microscopically to ensure that the colonies were of mycobacterium tuberculosis.

Results

In all 56 patients were observed, but in 26 it was impossible to complete the investigation because 11 were discharged from the sanatorium, five died and 10 became negative on culture during the period of investigation. Of the remaining 30 patients 25 are resistant to isoniazid, some up to 200 mcgm./cc., and their resistance is steadily increasing from test to test.

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The remaining five of the 56 patients reversed their resistance, four of them gradually, and one abruptly.

Resistance of these five patients' bacilli regressed from about 1 to 6 mcgm. Isoniazid/cc. level of resistance to a normal sensitivity, the growth of the organisms being inhibited by 0.02 mcgm. Isoniazid/cc. Before this phenomenon is discussed, a brief summary of the patients' histories is presented.

Case 1: F.L. A 44 year old female, was admitted to Wooroloo Sanatorium in 1949, with 10 months' history of cough, sputum and huskiness of voice. On x-ray film a cavity 5 cm. in diameter was seen in the right upper lobe, with abundant spread to the lower part of the right lung and the left middle zone. On bed rest and streptomycin 1 gm. daily, an extensive increase in the disease in the left mid-zone appeared after one month, and para-aminosalicylic acid was added to the streptomycin treatment. On March 3, 1950 a marked improvement was noted on the x-ray film. On April 15, 1950 streptomycin and P.A.S. was ceased after three months' combined course. On June 16, 1950 the cavity in the right upper zone appeared larger, and continued to increase in size until, on March 5, 1951, Monaldi drainage was instituted with intracavitary instillation of 2 cc. P.A.S. solution twice daily, with marked diminution in the sze of the cavity. Monaldi drainage was discontinued on April 30, 1951 and streptomycin and P.A.S. treatment recommenced. Just prior to right apicolysis with plombage, using lucite spheres, the cavity became larger and after operation a fresh spread to the left mid-zone was noted. On June 27, 1951 conteben treatment commenced. On January 21, 1952 right pneumonectomy was performed, followed by a broncho-pleural fistula and a widespread broncho-pneumonia on the left side. On June 17, 1952 all other chemotherapy was discontinued and isoniazid commenced. Improvement in her general condition occurred, the empyema space became smaller and the left lung partially cleared, in spite of the fact that the organisms grown on culture from her sputum and sinus discharge gradually became more resistant to isoniazid, finally reaching resistance to 6.0 micrograms per cc. Streptomycin and P.A.S. were added to the isoniazid on December 3, 1952 and by December 19, 1952 isoniazid resistance had fallen to the level of 0.24 micrograms per cc., and by January 16, 1953 her organisms were sensitive to isoniazid. In the x-ray film taken on February 4, 1953, clearing of the left lung was more marked. Throughout her sanatorium treatment she has been positive on direct smear or culture.

Case 2: D.D. A female of 47 years, was admitted to Wooroloo Sanatorium on February 22, 1948 with advanced bilateral pulmonary tuberculosis, with several cavities in the right upper lobe. She was treated conservatively on sanatorium regime until October 7, 1950, when P.A.S. was commenced. On March 12, 1952 conteben was added to the P.A.S. but no appreciable change in the x-ray films was noted. In July 1952 she appeared moribund, with gross oedema, ascites, and a markedly enlarged liver. She was taken off P.A.S. and conteben and given isoniazid. Her general condition improved dramatically, and on x-ray film some exudative lesions disappeared. Her sputum was positive on direct smear, and on September 26, 1952 the organisms were still sensitive to isoniazid. Subsequently, however, isoniazid resistance developed until December 19, 1952 when the organisms were resistant to 1 microgram per cc. of medium. On December 15, 1952 streptomycin and P.A.S. were added to the isoniazid, and by March 17, 1953 the large cavity in the right lung was reduced in size, the patient was comfortable and the quantity of sputum diminished, although remaining positive on direct smear. By January 30, 1953, however, the resistance of her organisms had decreased to a level of 0.24 micrograms per cc., and on February 20, 1953 they were isoniazid sensitive.

Case 3: M.S. A female patient of 45 years was admitted on October 19, 1952 with symptoms of some years duration. She had never consulted a doctor until her admission to the sanatorium. She presented as a case of far advanced bilateral pulmonary tuberculosis, with several cavities and with a wide bronchogenic spread. On admission she was in a desperate general condition. She was immediately given combined streptomycin and P.A.S. and isoniazid treatment. Her general condition during the last five months has improved considerably and x-ray films show regression of the exudative disease. She is still on combined chemotherapy. Her sputum was positive on direct smear on admission and remained so on culture until December 30, 1952, when she converted on ordinary Loewenstein culture, but two further sputa were positive on Loewenstein medium containing isoniazid on January 16 and January 31, 1953 (tests for isoniazid resistance). By November 21, 1952 her sputum contained organisms resistant to 0.06 micrograms per cc., and on December 19, 1952 the organisms were resistant to 6.0 micrograms per cc. On December 31, 1952 the level of resistance had fallen to 0.6 micrograms per cc., on January 16, 1953 to 0.24, on January 31, 1953 to 0.06, and on February 20, 1953 there was no growth on any culture medium.

Case 4: F.B. A male of 62 years was first admitted to the sanatorium on December 14, 1949 with one year's history of general lassitude, cough, sputum, loss of weight and appetite. He had a right upper lobe process with possible cavitation and he was treated on sanatorium regime. He absconded on September 24, 1950 and was re-admitted on December 30, 1950 with obvious cavitation in the right upper lobe. He started streptomycin and P.A.S. on March 13, 1952, but because of nausea and vomiting the P.A.S. was discontinued after one month and replaced by conteben. On August 12, 1952 he was taken off streptomycin and conteben and commenced on isoniazid. On February 4, 1953, in addition to isoniazid, streptomycin and P.A.S. were resumed, but on February 20, 1953, because of reaction, streptomycin was discontinued. Since 1949 his sputum has been consistently positive on direct smear or culture. His organisms became resistant to 0.6 micrograms of isoniazid per cc. of culture medium on September 26, 1952, six weeks after the institution of isoniazid and remained so until November 21, 1952. The cultures of December 19, 1952 and January 16, 1953 were contaminated, but on February 16, 1953 the organisms were again sensitive to all dilutions of the agent.

Case 5: S.K. A 60 year old male, was admitted to Wooroloo Sanatorium on November 28, 1951 with a four years' history of tuberculosis for which no active nor chemotherapeutic treatment had previously been given. He had had a recent large haemoptysis, and on admission his general condition was poor, with loss of energy, lassitude, cough, sputum and severe pain in the chest. His x-ray film showed atelectatic right upper lobe, with a large cavity in the middle zone and disease in the left lung. Streptomycin and P.A.S. were commenced and maintained until October 9, 1952, when they were replaced by isoniazid. On January 22, 1953 streptomycin and P.A.S. were added to the isoniazid. His sputum throughout treatment has been positive on direct smear. Resistance to 0.6 microgram of isoniazid per cc. of medium had developed by November 21, 1952, six weeks after the commencement of treatment, and by January 30, 1953 it had increased to the level of 1 microgram per cc. By February 19, 1953 his organisms were again isoniazid sensitive.

Discussion

Some writers have demonstrated that streptomycin resistance of mycrobacterium tuberculosis is not a constant property but may vary considerably without the institution of any other treatment. It has also been demonstrated that the combined use of chemotherapeutic agents diminishes

the likelihood of the appearance of resistant strains,[1,2] and further, that the continuation of treatment with the agent, against which the bacilli have already developed a certain degree of resistance[5] is not contra-indicated.

In some cases under observation in this survey, when isoniazid resistance developed, streptomycin and P.A.S. were re-introduced and led to fairly rapid disappearance of isoniazid resistant strains from their sputum, despite the fact that these drugs had not previously been effective in converting the sputum. Whether the reduction of the resistance level is permanent or temporary, requires further study and observation.

In three of the cases described above, the regression of the resistance is most probably related to the addition of streptomycin and P.A.S., in spite of the fact that Case 1 already presented a low degree of resistance against streptomycin, but was still sensitive to P.A.S.

In Case 2 it is obvious that streptomycin and P.A.S. treatment had a role in the reversion of the resistance to the normal level, a marked drop being noted six weeks after streptomycin and P.A.S. therapy was instituted; analysing this case the suggestion arises that the reversion of resistance may occur without the intervention of additional chemotherapy.

Case 3 is a bacteriological paradox; after one month of combined chemotherapy (streptomycin, P.A.S. and isoniazid) she developed isoniazid resistant organisms, the resistance increased to 6 micrograms isoniazid per cc. during the next four weeks and then gradually diminished, the organism finally becoming fully sensitive after four months of chemotherapy. In this case it is difficult to find a reasonable and acceptable explanation for the appearance and disappearance of the resistant strains. It is suggested that the abundance of organisms present initially, in the presence of gross caseous lobar and broncho-pneumonic disease, associated with the patient's apparently hopeless general condition, resulted in the rapid development of tolerance to the drug, although there was a gradual, progressive improvement in her clinical state.

The effect of streptomycin and P.A.S. is of course by no means instantaneous in the conversion of sputum, and another alternative is that these agents, to which in combination the development of resistance is a slow process, have in due course succeeded in eradicating the (isoniazid resistant) organisms from the sputum.

On culture tubes containing isoniazid (0.06 micrograms per cc. and 0.24 microgram per cc.) we obtained growth from the sputum, but the inoculum put up on ordinary Loewenstein medium on the same day did not show any growth. Unfortunately we were unaware at that time of the negative results of the routine sputum tests, and positive cultures from December 19, 1952 and January 16, 1953 were not retained. It is therefore not possible to prove that the strain of organism cultures was actually isoniazid dependent. If however, the existance of streptomycin dependent mycobacterium tuberculosis is accepted, it is not unreasonable to assume that isoniazid resistance will also develop.

In Case 4 it is difficult to draw any conclusion, because between No-

vember 1952 and February 1953 there were two series of contaminated culture tubes; streptomycin and P.A.S. were started on February 4, 1953 and by February 20, 1953 reversion of the resistance had occurred. We have to note that this patient from February 4, 1953 to February 20, 1953 had only 5 gms. of streptomycin. It is doubtful if such a quantity is able to have any influence on reversion of resistance.

In Case 5 the disappearance of the resistance more or less coincides with the beginning of the combined therapy, so that this may have had an important role in producing reversion of the resistance.

Conclusions

In a review of patients who developed isoniazid resistant strains of mycobacterium tuberculosis during the last six months, five out of 56 patients were discovered in whose sputum resistant organisms again became sensitive to isoniazid. The disappearance of resistant strains occurred in most cases after commencement of additional streptomycin and P.A.S., but in one case the reversion could possibly have occurred without the assistance of these agents. In one case we noted the appearance of colonies in culture tubes containing isoniazid, when cultures of that patient were negative on normal Loewenstein medium. This fact is suggestive that in certain cases isoniazid dependent organisms may develop.

SUMMARY

Isoniazid resistance of the mycobacterium tuberculosis is reversible in vivo, either by addition of other chemotherapeutic agents or possibly spontaneously. There is a suggestion of existence of isonicotinic acid hydrazide dependent mycobacterium tuberculosis.

RESUMEN

La resistencia a la isoniacida al micobacterium tuberculosis es reversible en vivo, ya sea por el agregado de otros agentes quimioterápicos o posiblemente de manera espontánea. Hay una sugestión de que existe bacilo de Koch dependiente de hidracida del ácido isonicotínico.

RESUME

La résistance du bacille de Koch à l'isoniazide est réversible *in vivo*, soit par l'addition d'un autre agent chimiothérapique, soit même spontanément.

On peut supposer qu'il existe des bacilles tuberculeux dépendants par rapport à l'isoniazide.

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Effect of the Isoniazide on Guinea Pigs Infected with Isoniazide Resistant Strains of Mycobacterium Tuberculosis*

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Introduction

The task of our present investigation was to demonstrate the action of isoniazide, if any, upon the isoniazide resistant strains of mycobacterium tuberculosis. We endeavored to find the level of resistance beyond which the drug is no longer effective and no clinical improvement is to be expected.

It is a well known fact, that a relatively high percentage of patients, treated by isoniazid after the elapse of a certain period of time, or after a certain quantity of medication develop tubercle bacilli which are resistant to this drug.[1-3] We tried to demonstrate this fact by using guinea pigs as experimental animals.

Methods

We had six groups of guinea pigs, each consisting of two individuals. The guinea pigs were approximately of the same age and weight (400 gms.). We infected all six groups with 0.1 mgm. of tubercle bacilli obtained from colonies grown on Loewenstein-Jensen medium. One of the strains was sensitive to isoniazide, the others were resistant for different strengths of isoniazide concentration. We considered the first group a control, the individuals of which were infected with isoniazide resistant strain (100 mcgm./cc.). The groups 2, 3, 4, 5, and 6 were infected with approximately the same quantity of mycobacterium tuberculosis, but of different degrees of resistance.

The individuals of the second group were injected with a strain cultured from sputum of a patient who had never been treated with any anti-tuberculous chemotherapeutic agent and whose bacilli had been proved sensitive to isoniazide, i.e. it had not been possible to subculture them in presence of isoniazide in concentration of 0.02 mcgm./cc. The third group was inoculated with micro-organisms resistant to isoniazide in concentration of 0.1 mcgm./cc. The fourth group was infected with a strain resistant to 1 mcgm./cc., the fifth group received injection with bacilli resistant to 20 mcgm./cc. and the sixth group was infected with mycobacterium tuberculosis resistant to isoniazide up to the concentration of 100 mcgm./cc.

The infected guinea pigs were injected subcutaneously in the right inner thigh on the same day, with approximately the same quantity of micro-organisms and kept in separate cages from the moment of inoculation.

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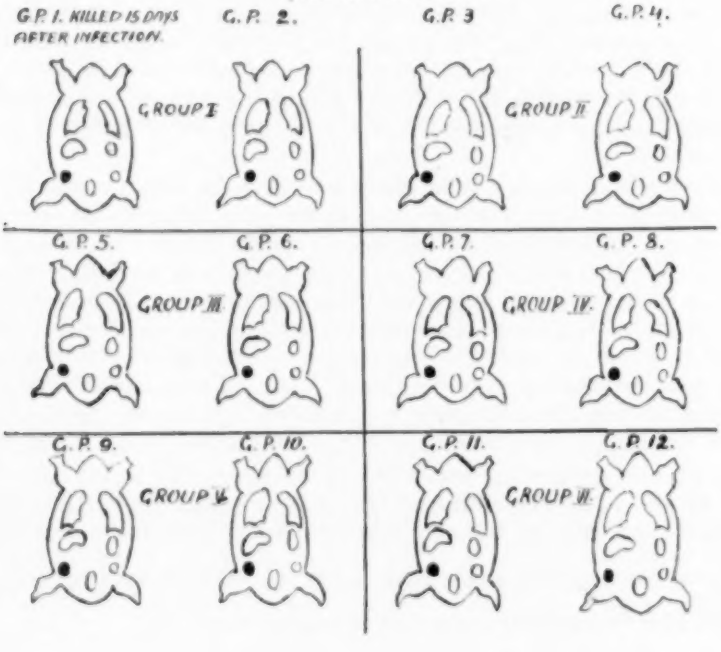
We provided them with similar food and living conditions. Their food consisted daily of 1 oz. of dry food with the following composition: 10 per cent whole wheat, 40 per cent bran, 40 per cent crushed wheat, 5 per cent meat meal, 2½ per cent bone meal, 2½ per cent buttermilk, for every kilogram weight of dry food one teaspoonful of common salt was added. For green food and water we gave them lettuce and carrots, the quantity varied with the temperature of the air and the animals demand.

The first group served as controls and was not treated, but one of the two guinea pigs were killed on the 15th day after inoculation, to verify the progress of the infection. The other animals were examined clinically (see diagram No. 1) and we found that everyone had lymph node involvement and the animals already presented general symptoms, consisting of loss of weight and diminished appetite. The sacrificed guinea pig (first group) presented major caseation and enlargement of right inguinal lymph nodes and an enlarged para-lumbar lymph node. From the caseous lymph node we were able to demonstrate acid fast bacilli, whose size, shape and staining behavior were characteristic of mycobacterium tuberculosis.

Beginning with the 15th day, the animals of the 2-6 groups were given isoniazide, with a dose of 4.4 mgm. per kilogram of bodyweight for 10 days, after which the dosage was increased to 6 mgm. per kilogram. Fifty per cent of the drug was given orally mixed with dry food and 50 per cent by daily hypodermic injections.

DIAGRAM NO. 1.



Results

In three to four days from the beginning of treatment we noticed that the appetite of the animals in the treated groups improved considerably, so that we had to increase the quantity of dry food to one and one-half ounces per day.

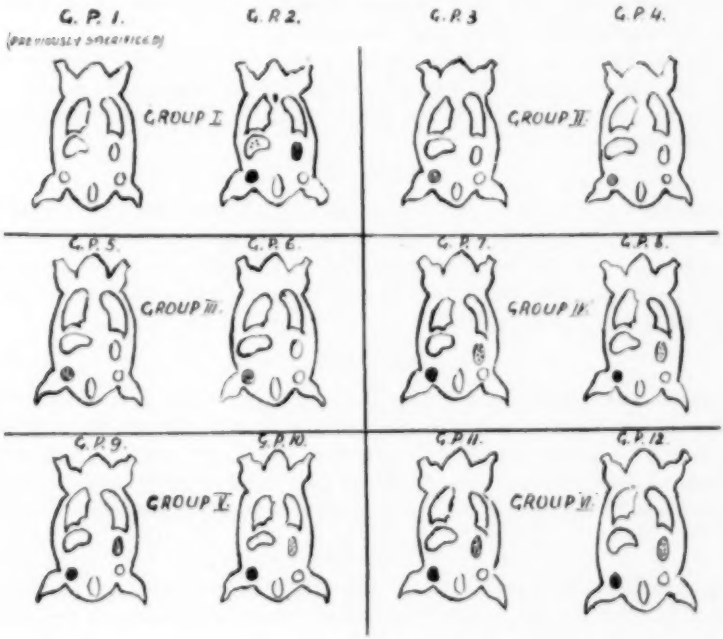
On the 15th day we examined the animals, but no significant change was found in the clinical picture, except that the treated animals ceased to lose weight.

After six weeks of treatment the animals were killed and examined. The results of examination are summarized diagrammatically in diagram No. 2.

According to diagram 2, the treatment was successful up to group 3. If we compare the pathological alterations in groups 4, 5, and 6 with the alterations of group 1 we still find that a certain difference exists between these groups. The spread of the disease in the treated groups (4, 5, 6) is not as advanced as in the untreated group 1.

The lymph nodes of the guinea pigs were examined microscopically in an endeavor to demonstrate the difference, if any, in the various groups, but no essential difference was demonstrable, between the treated and non-treated groups.

DIAGRAM No 2.



Discussion

It has been demonstrated by various writers, that patients treated by streptomycin after a lapse of time develop streptomycin resistant organisms. If the resistance reaches the level of 50 to 100 mcgm./cc. and the patients are further treated with the same antibiotic, it fails to improve the condition of the patients. On the other hand the survival of the guinea pigs infected by streptomycin resistant organisms treated by streptomycin and the untreated control groups did not show any marked difference.[4-6] Other writers demonstrate that some clinical improvement could be achieved most probably owing to the fact that an increased acquired resistance occurs as a consequence of the distruction of the still sensitive strains.[5] As we demonstrated above, the animals infected with organisms resistant to 1 mcgm. isoniazide/cc. or with micro-organisms with higher resistance than that do not respond markedly to the treatment with isoniazide or in any case not in such degree to justify the continuation of the treatment. For instance in group 2 during the treatment a generalization of the tuberculosis did not occur, the process was localized to the regional lymphatic nodes, macroscopically a certain regression was noted. On the other hand in groups 4, 5, and 6 an involvement of the spleen was evident as a sign of generalization of the tuberculous process.

Knowing that the type of tuberculosis developing in the guinea pig differs from that in the human, so the problem arises that the above statement which applies to the guinea pig may not be applicable to human tuberculosis, which develops on a substratum with a certain inborn and acquired resistance. This is a matter which has to be considered and requires further careful study and observation.

If the therapy were maintained for a longer period the difference between the groups might be more marked and further improvement could occur in the treated groups. These problems are under current investigation in this laboratory.

SUMMARY

Isoniazide administered for six weeks in the treatment of tuberculosis of the guinea pig infected with isoniazide resistant mycobacterium tuberculosis is effective to the resistance level of 1 mcgm./cc. Above this degree of resistance the progress of the disease is delayed in comparison with the non-treated control animals.

RESUMEN

La isoniacida administrada por seis semanas en el tratamiento de la tuberculosis en cuyos infectados con microbacterias tuberculosis resistentes a la isoniacida, es efectiva a una concentración de 1 mcgm./cc. Sobre este grado de resistencia la evolución de la enfermedad es retardada en comparación con la observada en los animales de control no tratados.

RESUME

Chez les cobayes inoculés avec des bacilles tuberculeux résistants à l'isoniazide, l'action du traitement par ce produit administré pendant six

semaines reste efficace lorsque le taux de résistance ne dépasse pas un gamma par cc. Au-dessus de ce degré de résistance, l'évolution de l'affection est simplement prolongée par rapport à celle des animaux témoins non traités.

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A Study on Therapeutic Evaluation of Isoniazid in Treatment of Pulmonary Tuberculosis

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Clinical studies of the hydrazid derivatives of Isonicotinic Acid were initiated at Eastern North Carolina Sanatorium on April 5, 1952. This investigation was directed toward therapeutic evaluation and toxic effects of this drug.

Materials

Ninety-two patients were studied. Almost all had extensive, active, pulmonary tuberculosis. Many of them had previously been given one or more of the currently accepted treatments and all patients had positive sputum.

Classification of the pulmonary status and other details of the pre-study period of these patients are to be found in Table I.

TABLE I

	Number of Cases
Total Number of Cases	92
Male	60
Female	32
Race, Age	
White	61
Colored	31
Average age	45.7
Classification of Their Pulmonary Tuberculosis	
Far advanced	71 - 77%
Moderately advanced	20 - 21%
Minimal	1 - 1%
Previous Duration of Disease	
6 months	20
6 to 12 months	19
1 to 2 years	31
2 years and more	22

Isoniazid has been given to two patients for 11 months, to 82 for nine months, and to eight for five months (Table II).

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TABLE II

Type of INAH Therapy

Type	Number of Cases
Cases Given INAH Alone	29
Cases Having Had No Other Drug	6
Cases Given INAH and Streptomycin	9
Cases Given INAH, Streptomycin, and PAS	54
Duration of INAH Therapy	
Cases Given INAH for 11 Months	2
Cases Given INAH for 10 Months	82
Cases Given INAH for 5 Months	8

Most of the patients are still on isoniazid. The dose was standardized at three to four milligrams per kilogram. It was given twice daily, one dose in the morning before breakfast, the other at bed time.

In the group treated with dihydrostreptomycin, isoniazid and PAS combined, almost all patients (except the two with miliary disease and the two with meningitis received one gram of streptomycin twice a week and 12 grams of PAS daily.

Results

A) *On General Condition:* Since the great majority (77 per cent) of the cases were far advanced, the first result of therapy was seen on general condition and clinical signs. Toxic systemic manifestations such as temperature elevation, asthenia, anorexia, weight loss, and malaise, showed in general significant amelioration within two or three weeks after isoniazid was started. Likewise, there was less sputum and cough, increase in appetite, gain in weight, and a feeling of well being.

In 17 of the 92 cases (19 per cent) marked improvement was noted. In 40 (43 per cent) slight symptomatic improvement was noted. Eight (8 per cent) showed slight temporary improvement. In 21 (23 per cent) the general condition was unchanged and six cases (6 per cent) became worse while on therapy (Table III).

TABLE III: RESULTS OF ISONIAZID TREATMENT

A. *General Condition*

Condition	Number of Cases
Markedly Improved	17
Improved	40
Temporarily Improved, Then Relapsed	8
Unchanged	21
Worse	6
B. *Sputum*	
Negative at Administration of Drug	11
Converted to Negative in Smear	12
Temporarily Negative in Smear	18
Remained Positive	51

The first two patients were put on isoniazid at the beginning of April 1952. They were not told what they were being given, thereby eliminating any psychological effect of receiving the drug. Both of these patients were in a toxic condition, having far advanced, extensive, bilateral disease. Within three weeks an almost dramatic amelioration began.

Eighty-two were placed on isoniazid on May 6, 1952. In the great majority of this group (65 cases) improvement (moderate and mild) has been observed. It is interesting to note that six of them showed significant prompt and temporary elevation of temperature for the first five or six days (Table VI) and then experienced a decline in temperature which remained normal with continuation of therapy.

The group showing temporary improvement (eight cases) and many of the others showed late recurrence of fever and other symptoms of tuberculosis after an average of five or six months period of therapy (Table III). Defervescence was accompanied by an equally rapid reverse of toxic manifestation. On the other hand recurrence, also, was accompanied by parallel, progressively increasing toxic manifestation of tuberculosis. This was explained as a possible development of resistance; in other words, multiplication of non-sensitive microbacteria. Signs of improvement such as a sense of well being, improved appetite, return of strength and energy, were the earliest results of isoniazid therapy. Weight gain followed in about three or four weeks of treatment. Among this group of 65 maximum weight gain was 38 pounds, minimum weight gain was eight pounds, and the average was 12 pounds.

B) *Effect on Cough and Sputum:* Significant decrease in cough and in amount of sputum has been noticed. In 12 (13 per cent) the sputum became negative on smear; only three were negative by culture. In 11 previously positive, sputum was negative at the beginning of drug administration.

In 18 (19 per cent) sputum smears became negative temporarily. In the great majority (51 cases or 55 per cent) sputum smears remained positive, although a decreased count was reported (Table III).

C) *X-ray Changes:* Obviously x-ray film observations were made in all cases. Periodic films did not reveal changes comparable to those observed in the general condition of the patients. Complete x-ray film clearing was not seen in our series. Twenty-three (25 per cent) showed slight improvement. Seventeen (18 per cent) were markedly improved. In only two did a cavity disappear and 32 (35 per cent) were unchanged. On the other hand 10 patients changed for the worse. Of the 17 cases showing marked improvement, 10 (58 per cent) were given combined therapy consisting of streptomycin, para-aminosalicylic acid, and INAH. Many cases in the group showing slight improvement became worse within five to six months after administration of isoniazid, even though their general condition continued to improve. Of the 17 mentioned above as markedly improved, one with bilateral cavitation and with bacilli resistant to dihydrostreptomycin showed the cavity on one side closed, and it was possible to do lobectomy on the opposite side. This patient's tuberculosis remains stable

six months after surgery in spite of the fact that isoniazid was discontinued immediately after the operation because of suspected toxicity which will be mentioned later. In another case, acutely ill with extensive, exudative infiltration in the right upper and left lower lobes, isoniazid was given alone. Marked improvement took place, both radiologically and clinically, for the first eight months; but after that the sputum, which had become negative for a short time, again became positive and there was no further x-ray film change. In the third case a cavity disappeared roentgenologically (Table IV).

TABLE IV: X-RAY CHANGES

Type of Therapy	Total No. of Cases	Improved No.	Improved Pct.	Markedly Improved No.	Markedly Improved Pct.	Cavity Gone No.	Cavity Gone Pct.
INAH Alone	29	9	(31)	5	(17)	2	(6)
INAH & Strept.	9	4	(48)	2	(23)		
INAH, Strept. & PAS	53	10	(18)	10	(18)		

TABLE IV (Continued)

Type of Therapy	Total No. of Cases	Unchanged No.	Unchanged Pct.	Worse No.	Worse Pct.
INAH Alone	29	10	(34)	4	(13)
INAH & Strept.	9	3	(33)		
INAH, Strept. & PAS	53	27	(50)	6	(11)

On the other hand, in four cases new cavities appeared. In three enlargement of old cavities occurred. In two the appearance of new exudative disease occurred during isoniazid treatment.

D) *Extra-Pulmonary Tuberculosis* (six cases): These cases, so classified, all had some degree of pulmonary tuberculosis in addition. In two cases of tuberculous meningitis, one of empyema, and one of bronchopleural fistula, isoniazid has been used with streptomycin and para-aminosalicylic acid. The one with bronchopleural fistula and empyema improved and lobectomy was done on that side. Good results were also noted in one case of tuberculous orchitis and in one of tuberculous fistula-in-ano (Table V).

TABLE V: EXTRA-PULMONARY TUBERCULOSIS

Diagnosis	Number of Cases
Tuberculous Meningitis	2
Tuberculous Empyema	1
Bronchopleural Fistula and Empyema	1
Orchitis	1
Fistula-in-ano	1

Toxicity

In cases receiving isoniazid, the cephalin flocculation test has been used for liver function; and urine, blood and sputum examinations have been done routinely. All systems were watched closely for signs of intoxication. Some toxic effects have been noted (Table VI). For instance, in one case which showed satisfactory roentgenological results, bilateral peroneal palsy

TABLE VI: DRUG TOXICITY

Toxic Manifestations	No. of Cases	Drug Discontinued	Drug Continued
Persistent Liver Function Disturbance. 4+ * Cephalin Flocculation Test	4	4	
Micturition	2	1	1
Bilateral Peroneal Palsy	1	1	
Peripheral Neuritis (in both legs)	1		1
Urticaria	1	1	
Hyperleukocytosis	6		6
Mental Depression	6	4	2
Suicide	1	1	
Attempted Suicide	1		1
Elevation of Temperature	6		6
TOTAL	29	12	17

with muscular atrophy occurred immediately after excisional surgery. It is true that this individual is neurotic but he has developed an organic neurological complication. In this case general anesthesia can be suspected of having precipitated the toxic side effect of the drug. In another case, also, similar trouble was seen right after surgery, but it was neither as severe nor as permanent. One case given isoniazid prior to surgery developed paranoid obscessions right after surgery and continued for approximately two months. Also, in this case surgical shock or general anesthesia can be suspected.

Six developed mental depression, one of whom committed suicide. A second attempted suicide, and two of the others had a complete depressive psychosis, e.g. symptoms abated when drug was discontinued and returned upon giving the drug again. In four other cases some personality changes occurred. They became almost childish, un-cooperative. In two cases difficult micturition has been seen.

Other toxic symptoms appeared as follows:

In six cases temporary initial rise in temperature; in six leukocytosis (between 20,000 - 25,000); in one urticaria developed; in four cephalin flocculation test was 4+, and, because of this, drug administration was discontinued. Urine tests showed no change and no failing kidney function.

In five antihistaminic drugs were given during isoniazid therapy and in

none of them was there evidence of incompatibility. Administration of prostigmine bromide did not relieve difficult micturition in the two cases in which it was tried.

In a great majority of cases side effects due to drug toxicity appeared early in the course of treatment, almost all by the third or fourth week. In some cases toxic symptoms cleared after the drug was stopped, and did not reappear when it was started again; but in others the opposite was true.

Results from Drug Combinations

Twenty-nine of the 92 cases were given isoniazid alone. Six of them had had no previous chemotherapy. Nine of the 92 were given isoniazid plus streptomycin. Fifty-four of the 92 were given all three drugs, i.e. streptomycin, isoniazid, and PAS (Table II). The cases given isoniazid and streptomycin showed the highest percentage of x-ray improvement, nine of these in all; four of them (48 per cent) showed slight to moderate improvement, and two (23 per cent) marked improvement in x-ray film and general condition.

Comment

Even though a number of studies have been published, it is thought that more knowledge and more experience coming from several and different sources is needed on this subject. Also, we believe that every investigator should continue to publish his own experiences until we can get a much more crystallized opinion. In the past 10 years great advancement in the treatment of tuberculosis has taken place, both medical and surgical. Changes have occurred rapidly; but more investigations, more observations, and more time will be required before the underlying realities can be finally determined.

This clinical study reveals isoniazid as another useful weapon in the treatment of tuberculosis, but not the final answer. In other words, the result of this investigation has not proved that isoniazid can sterilize host organisms from acid-fast bacilli. Even in the dose of three to four milligrams per kilo used in this series of cases, certain significant toxic side effects occurred. Sensitivity studies were not available, but the clinical course, x-ray film examinations, and sputum studies have given the impression that resistance to isoniazid may develop within five to six months.

Early clinical effect has been seen in amelioration of the systemic toxic reactions so common in tuberculosis. Then improvement of respiratory symptoms was observed. X-ray film clearing was not as satisfactory as was the symptomatic improvement. The number of bacilli was reduced in the sputum smears temporarily and in some cases remain negative, this in 13 per cent of the cases. In the others the bacillary count was often reduced at least temporarily and some were negative for periods of two to three months only to become positive again.

Isoniazid offers new hope for all tuberculous patients, but especially for streptomycin resistant ones in need of further medical or surgical treatment. It is relatively inexpensive. There is also the advantage of being able to give it orally without causing a serious gastrointestinal disturbance.

General experience recommends using isoniazid in connection with another anti-tuberculosis drug, to prevent early resistance.

The toxicity of isoniazid is a problem, in some cases indicates discontinuation (12 out of 92). Serious central nervous system side effects are more common in persons who have unstable personality or history of previous psychotic episodes or previous convulsive disorders. Toxic side effects have been seen in other systems of the body, but they were not so serious.

SUMMARY

Isoniazid has been given to 92 cases in the Eastern North Carolina Sanatorium starting April 4, 1952, for a five to 11 months period. The great majority had received streptomycin and PAS previously. These investigations were directed toward the evaluation of therapeutic and toxic effects of the drug.

Because the great majority of the studied cases (77 per cent) were far advanced, the first results of therapy were seen on the general condition. Relief of the common toxic symptoms of tuberculosis occurred early. Specific respiratory symptoms were slower. Systemic toxic manifestations of tuberculosis ameliorated almost dramatically within three to four weeks. In the following phase respiratory signs were diminished. X-ray film changes were not as significant as was the clinical improvement.

Clinical, and in some cases roentgenological, improvement gradually increased for about five or six months, after which there was either no further change or there was evidence of relapse.

Toxicity of the drug, especially on the central and peripheral nervous systems, is reported.

RESUMEN

Se ha usado isoniacida en 92 casos en el Sanatorio del Noreste de Carolina del Norte, empezando en Abril 4 de 1952 y por 5 a 11 meses de duración. La gran mayoría habían recibido estreptomicina y PAS antes. Estas investigaciones se orientaron hacia la valuación de los efectos terapéuticos y tóxicos de la droga.

Como la mayoría de los casos estudiados (77 por ciento) eran muy avanzados, los primeros resultados fueron observados en el estado general. Pronto ocurrió el alivio de síntomas tóxicos comunes.

Más lentamente mejoraron los síntomas respiratorios propios de la tuberculosis. Las manifestaciones tóxicas generales mejoraron casi dramáticamente dentro de tres a cuatro semanas. En la fase siguiente los signos respiratorios disminuyeron. Los cambios radiológicos no fueron tan significantes como los clínicos.

La mejoría clínica y en algunos casos la radiológica aumentó gradualmente por 5 o 6 meses aproximadamente después de los cuales ya no hubo cambio o hubo recaída.

La toxicidad de la droga especialmente sobre los sistemas nerviosos central y periférico, se refiere.

RESUME

L'isoniazide a été donnée à 92 malades dans le Sanatorium de la Caroline du Nord-Est, à partir du 4 avril 1952 pendant une période de 5 à 11 mois. Dans la grande majorité, les malades avaient reçus antérieurement streptomycine et P.A.S. Les investigations eurent pour objet l'évaluation de l'effet thérapeutique et toxique de la drogue.

Etant donné que la grande majorité des cas étudiés (77%) étaient des formes de tuberculose très avancées, les premiers résultats du traitement portèrent sur l'état général. Précocément on assista à l'amélioration des symptômes généraux d'intoxication de la tuberculose. L'action portant véritablement sur l'arbre respiratoire fut plus lente. Les manifestations toxiques de la tuberculose s'améliorèrent d'une façon quasi théatrale, en trois ou quatre semaines. Dans un stade ultérieur, les troubles respiratoires diminuèrent. Les modifications radiologiques ne se montrèrent pas aussi nette que les améliorations cliniques.

Les symptômes cliniques et dans certains cas radiologiques s'améliorèrent graduellement pendant cinq ou six mois environ. Au bout de ce temps, il n'y eut plus d'amélioration ou il y eut au contraire apparition de rechutes.

L'auteur fait état de l'action toxique du produit, spécialement sur le système nerveux central et périphérique.

The Treatment of Tuberculous Meningitis in Infants with Streptomycin and Isonicotinic Acid Hydrazide (Isoniazid)*

A Preliminary Report of Six Patients Under the Age of Two Years Treated Without Intrathecal Medication.

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The addition of streptomycin to the therapeutic regimen has changed the natural history of tuberculous meningitis in both adults and children. This has been amply demonstrated in the case of children in the large series of patients treated by workers both here and abroad using streptomycin intramuscularly and intrathecally, usually in combination with a sulfone derivative. The universally fatal mortality of this disease has been markedly and significantly reduced by this method.[1-4,26,29,33]

Despite these accomplishments, there is still a great need for improvement of therapeutic results in tuberculous meningitis. The number of fatalities, and the degree and number of significant neurological residua, have made it incumbent upon the clinician to seek newer therapeutic agents or, at least, new combinations of existing anti-tuberculous agents. Furthermore, there are certain disadvantages to the use of streptomycin intrathecally. This method of medication is a cumbersome one, trying to the patient and the physician. It results in the introduction into the sub-arachnoid space of an irritating substance which may give rise to pleocytosis, fever, and convulsions,[5] confusing the clinical picture and temporarily increasing the degree of illness of the patient.

The preliminary studies of isoniazid in vitro[6,7] in animal experiments,[8-10] and in early clinical trials[10-13] indicate that it has an anti-tuberculous action of significant proportions. It has exhibited only minor toxicity and a low degree of pharmacodynamic side effects in animals and humans.[13-16] Its high degree of diffusibility makes it particularly useful where a high concentration of chemotherapeutic agents is required, particularly in body fluids. It has the property, unique in anti-tuberculous agents, of exerting a bacteriostatic effect on intracellular tubercle bacilli.[17] It was early demonstrated that the isoniazid molecule appeared in significant concentration in the cerebrospinal fluid.[16] It appears likely also, that the combination of this drug with streptomycin may forestall the emergence of isoniazid and/or streptomycin resistant strains of tubercle bacilli.[18,19]

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The Isoniazid used in this study was supplied by Merck & Company, of Rahway, New Jersey; C. Pfizer & Company, Brooklyn, New York, and Schering Corporation of Bloomfield, New Jersey. Sodium salt of PAS was supplied by Merck & Company of Rahway, New Jersey, and the Panray Corporation of New York City.
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Moreover, the recent work of Mackaness and Smith[32] presents rather definite evidence both in vivo and in macrophage cultures that the combined use of streptomycin and isoniazid may result in an acceleration of the death rate of intracellular and extracellular tubercle bacilli.

All of these properties of isoniazid make it particularly suitable for trial as an adjuvant agent in the treatment of tuberculous meningitis, both as a means of circumventing the use of intrathecal medication and also as a means of increasing the bacteriostatic effect of streptomycin.

Both in Europe and America, there have already appeared encouraging preliminary clinical evaluations of the effects of these agents, either alone or in combination with streptomycin in the treatment of tuberculous meningitis. The number of cases has been small, the periods of observation short and the age distribution of the patients variable. Klee[13] employed intrathecal isoniazid with beneficial results. Ragazzini and his colleagues[20] made use of isoniazid intrathecally in association with streptomycin and a sulfone. Sweetman and Murphy[21] treated one case with isoniazid alone with good results, and three with isoniazid following intramuscular and intrathecal streptomycin with equivocal results. All felt that results were sufficiently striking to justify further trial with these drugs.

Clark, et al.,[22] also report a favorable effect on tuberculous meningitis treated with isoniazid when used in combination with streptomycin, intramuscularly and intrathecally. They report on two cases treated with streptomycin and isoniazid without streptomycin intrathecally with encouraging results. Three of 10 treated with isoniazid alone died, in the first week of treatment. It was their feeling that isoniazid alone was not sufficient in the treatment of tuberculous meningitis but that its use with streptomycin might obviate the use of intrathecal therapy.

This present report is concerned with a preliminary evaluation of our experience with the treatment of tuberculous meningitis in six children under the age of two years. All have been treated from the outset, except the first case, with streptomycin intramuscularly and isoniazid by mouth or intramuscularly without the intrathecal use of either streptomycin or isoniazid. Their clinical and spinal fluid response was sufficiently impressive to make their reporting seem worthwhile as a preliminary indication that streptomycin and isoniazid when used in combination, may give results comparable to those obtained with the use of intrathecal and intramuscular streptomycin and promizole without the disadvantages of intrathecal therapy.

Material and Methods

This group consists of six children ill with meningeal tuberculosis, five females and one male, five white and one Negro, ranging in age from seven to 21 months. Diagnosis in each case was based upon: (1) history of exposure to a known case of pulmonary tuberculosis in the household; (2) positive tuberculin test,—in several cases following a previously negative test; (3) characteristic cerebrospinal fluid findings; (4) recovery of tubercle bacilli from the spinal fluid in three of the six and (5) x-ray film

evidence of pulmonary tuberculosis in all, two of them miliary. All had received some intramuscular streptomycin before admission. These courses were usually short and associated with interrupted use of PAS. Only one, D.M., had received streptomycin intrathecally totaling 10 injections of 50 mg. each. None had received isoniazid. All had shown progression of disease without response to therapy prior to admission.

Therapeutic Regimen and Scheme of Management

I. *Streptomycin:*

Streptomycin sulfate was given intramuscularly in a dose of 0.5 grams per day, irrespective of body weight until the spinal fluid had been normal for three months. Thereafter it was given in dosage of 0.5 gram three times a week.

II. *Isoniazid:*

In the first patient (D.M.) the dose of isoniazid was begun at 4 mg. per kilo and increased within a period of 10 days to 10 mg. per kilo. All others received from the beginning a daily dosage of 10 mg. per kilo. Whenever tolerated, this was given orally, mixed with solid or pureed food, and divided in three or four doses in 24 hours. Vomiting was common early in the course of treatment and when this occurred, intramuscular isoniazid (Cotinazin, Pfizer) was given also in divided doses. If vomiting occurred within one hour after an oral dose, an equivalent dose was repeated intramuscularly.

III. *PAS:*

This was given as the sodium salt mixed with pureed foods in divided doses for a total daily amount usually of 2 grams. PAS had often to be discontinued because of gastro-intestinal irritation and frequently the dose was cut in half or discontinued entirely for considerable periods of time to avoid serious fluid and electrolyte disturbances. PAS was re-instituted in those who could tolerate it, particularly during the period of convalescence. Two patients who could not tolerate PAS were put on promizole.

IV. *General Measures:*

Energetic nursing care, and special attention to nutrition were deemed to be of great importance. Feeding by intermittent gavage had often to be resorted to in the early stages of treatment. Dietary supplementation with high protein materials and vitamins was employed. In the early acute phase, careful attention to sedation was necessary. Tub baths were useful for sedation and muscular relaxation and to combat episodes of extreme hyper-pyrexia. The use of suction in maintaining an airway free of tracheo-bronchial secretions and the use of oxygen were often needed. Early attempts at muscular re-education were undertaken to prevent deformities associated with sustained muscular contractions.

Laboratory Data Used in Follow-up

A. Spinal fluid:

Spinal fluid examinations for cells, protein, and sugar were done weekly during the early course of treatment, but once the favorable direction of

clinical progress was determined, the number of spinal taps was reduced to one or two a month. Chlorides were determined only infrequently since our experience corresponded to that of Lincoln[23] in that this measurement was not found to be useful in following the course of the disease. Two consecutive spinal fluids were examined by smear and culture for tubercle bacilli before the initiation of therapy in each case. During the early months of therapy, cultures of spinal fluid for tubercle bacilli were done on frequent occasions. The number of these determinations also was diminished as the patient showed clinical improvement, since tubercle bacilli were obtained in only one case after the first month of therapy. Serial determinations of the plasma and spinal fluid levels of streptomycin and isoniazid, were performed in all at varying periods after an oral or intramuscular dose. Streptomycin levels were determined by the method of Stebbins and Robinson[24] and isoniazid levels by the method of Kelly and Poet.[25]

B. Complete urinalysis was performed once a week.

C. Complete blood and differential white counts were done twice a month.

D. Thymol turbidity, cephalin flocculation, and icteric index determinations were performed every two weeks during the course of therapy. Blood urea nitrogen was determined every three weeks.

E. Roentgenograms of the chest were obtained every two months.

F. Electrocardiograms were obtained at the beginning of therapy and repeated after three to six months of treatment.

Results

A. Clinical Responses:

These children have been under continuous treatment with the above outlined regimen for periods ranging from four to 13 months. Their clinical and cerebrospinal fluid response is summarized in Table I. At present, all are alive and have shown distinct improvement.

The responses in general clinical state and in signs of meningeal irritation were gradual but striking in all. No dramatic immediate responses were noted but in every case beginning usually within two weeks after the initiation of therapy, there was gradual diminution in muscular rigidity, improvement in the state of consciousness and complete cessation of convulsive seizures. Signs of meningeal irritation disappeared within two to four months after the beginning of treatment. In no case was there progression of the focal neurological signs or of the cerebral irritative phenomena after the start of treatment. In one case, P. S., after four months there occurred a complete left facial palsy. This slowly and almost completely disappeared after physiotherapy and continued treatment of the meningeal process.

Their general nutritional state followed improvement in the neurological sphere. There were none of the manifestations of voracious appetite such as have been reported in the isoniazid therapy of pulmonary tuberculosis in adults,[10,11] nor have there been any dramatic changes in weight. Weight

TABLE I: Summary of Clinical and CSF Findings in Six Cases of Tuberculous Meningitis Treated with Streptomycin and INAH Without Intrathecal Medication

Patient	Mos. of Observ. Under Rx., INAH and SM.	Previous Rx. Before Start of Combined Therapy	Clinical State At Start of SM and INAH Rx.	SPINAL FLUID — Before Therapy Cells	Proteins	Sugar	SPINAL FLUID — At End of Observation Period Cells	Proteins	Sugar	Clinical State at End of Observation Period
D.M. Male 16 mos.	13	3 wks. SM 0/5 G.I.M./day 50 mg. I.T. for 10 days	Comatose, status epilepticus; impairment of sight & hearing; hyperpyrexia; lt. abducens paralysis; dehydrated; malnourished; cyanotic; bilat. papilledema.	285	285	26	1	27	55	Clinical state excellent no focal or meningitic signs; hearing and sight seriously impaired but improved; mentally retarded; ataxic, unable to sit alone; afebrile 11 mos.; CSF normal 8 mos.
P.S. Female 16 mos.	11	DSM 0/5 G.O.D., IM for 3 wks.; no I.T. Rx.	Semi-comatose, generalized convulsions; impairment of sight and hearing; bilat. internal strabismus; bilat. papilledema, malnutrition; dehydration; gen. spasticity of limbs.	52	81	10	2	29	53	Clinical state excellent, no focal or meningitic signs; hearing and sight improved but still impaired; slight hydrocephalus since admission; mentally retarded; unable to sit alone; left facial palsy at 4½ mos. almost disappeared; scoliosis of spine evident at 6 mos. improved; afebrile 8½ mos.; CSF normal 8½ mos.
J.S. Female 7 mos.	10	DSM 0/5 G BID for 7 days; no I.T. Rx.	Associated miliary tuberc.; no focal or meningitic signs; febrile dehydrated; malnourished; cyanotic.	10 11	43 53	41 40	0	30	42	Clinical state excellent, no neurological abnormalities; all activities normal; afebrile 8 mos.; CSF normal 6½ mos.
				Tubercle Bacilli isolated on admission						

SM—Streptomycin. IT—Intrathecal. CSF—Cerebrospinal fluid.
DSM—Dihydrostreptomycin. IM—Intramuscular. INAH—Isonicotinic Acid Hydrazide.

TABLE I (Continued)

Patient	Mos. of Observ. Under Rx., INAH and SM.	Previous Rx. Before Start of Combined Therapy	Clinical State At Start of SM and INAH Rx.	SPINAL FLUID — Before Therapy Cells	Proteins	Sugar	SPINAL FLUID — At End of Observation Period Cells	Proteins	Sugar	Clinical State at End of Observation Period
L.L. Female 11 mos.	7½	SM 0/25 G 3 doses; no I.T. therapy	Semi-comatose; focal seizures; left abducens paralysis; gen. spasticity of limbs; impairment of sight and hearing; bilat. papilledema; malnourished.	250	140	26	2	57	52	Clinical state and nutrition excellent; no meningitic signs; abducens paralysis and strabismus less marked; anisocoria present; vision greatly improved; hearing normal; afebrile 6½ mos.
				Tubercle bacilli isolated on admission						
M.F. Female 21 mos.	6½	SM 0/4 G per day for 1 mo.; no I.T. Rx.	Comatose; sustained opisthotonus and extreme rigidity of extremities; lt. abducens paralysis; ptosis lt.; lt. facial paresis; bilat. papilledema; slight hydrocephalus.	27	94	30	4	22	54	Clinical state and nutrition good; hydrocephalus unchanged; focal signs absent; almost blind, deaf; aniscoria; afebrile 5 mos.; CSF normal for 2 mos.
				Tubercle bacilli isolated on admission						
D.P. Female Negro	4	SM 0/3 G per day for 21 days; DSM 0/3 G per day for 10 days	Hyperexia; no meningeal signs. Positive tuberculin test. Miliary and tracheobronchial lymph node tuberc. Nutrition fairly good.	104	64	27	3	26	48	Clinical state and nutrition excellent; entirely asymptomatic; activities normal; afebrile 3 mos.; CSF normal for 3 mos.

SM—Streptomycin. IT—Intrathecal. CSF—Cerebrospinal fluid.
DSM—Dihydrostreptomycin. IM—Intramuscular. INAH—Isonicotinic Acid Hydrazide.

gains have been gradual, and steady and between three and five months of therapy were required before their standard weight was attained. There were temporary setbacks in the weight pattern which were ascribed to frequent vomiting as the result of PAS administration, but when the dosage of this medication was reduced or excluded as soon as vomiting occurred, weight gains continued to rise progressively.

Careful clinical observations were made on the progress of focal neurological lesions. The extra-ocular muscle imbalance in the patients treated for a longer period (as D.M. and P.S.) has disappeared completely and required between four and six months of therapy to do so. Extra-ocular muscle imbalance in the cases of L. L. and M. F. has greatly diminished since admission but is still present. Examinations of the auditory and visual sense in this age group are extremely difficult to make objectively; however, during the course of therapy, several observers were asked repeatedly to make an independent estimate of these functions, on a grossly clinical basis. It was the general impression that none of these patients showed worsening of their visual and auditory senses during the course of therapy and that in those treated for the longer periods of time, as D. M. and P. S., there had been slight but definite improvement in both these sensations.

As these children emerged from their clouded sensorial states and as they lost their muscular rigidity and spasticity, they all evidenced great weakness of all the major muscle groups. This weakness responded gradually to early physiotherapy and there was progressive return of normal muscular motion.

B. Temperature Course:

There were no dramatic temperature responses such as have been noted in occasional patients in the preliminary studies of meningeal or pulmonary tuberculosis reported by others. The earliest return of temperature to normal was observed in the case of L. L., who had defervescence after one week of therapy. The average length of time required for a return of temperature to normal was between three and six weeks. The fall in temperature was gradual over this period and this was followed by another period of four to six weeks in which there were occasional recrudescences of fever of mild degree usually lasting only a day or two without any accompanying clinical change. All patients are afebrile at the time of this report.

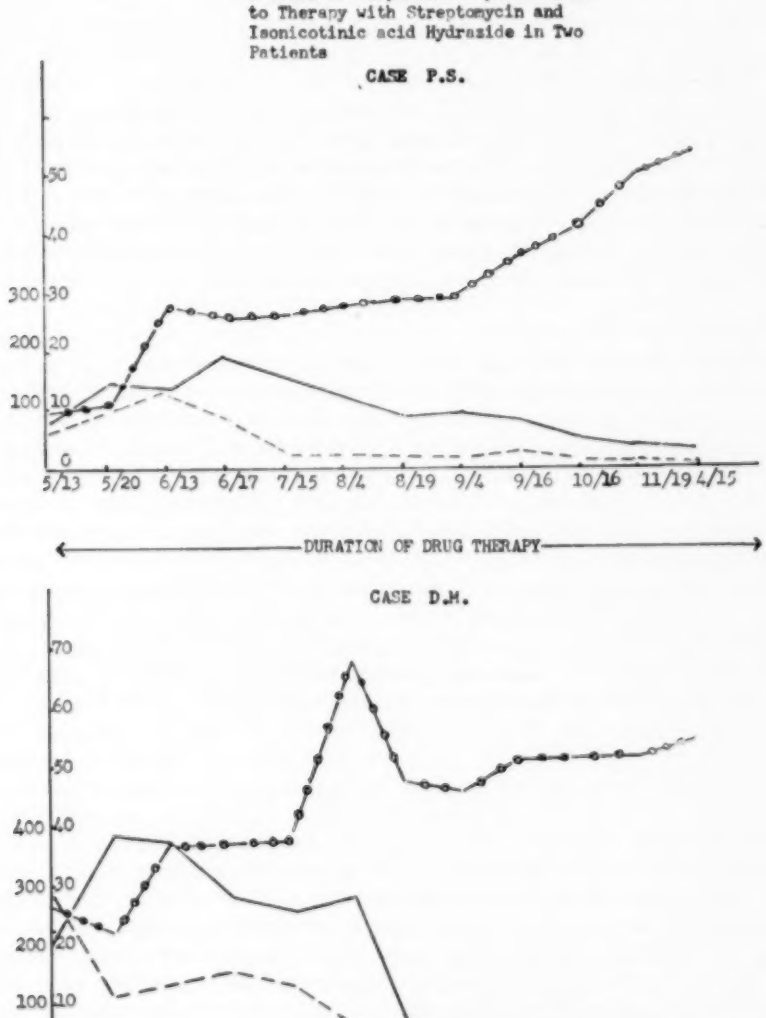
C. Cerebrospinal fluid course:

The response in the cerebrospinal fluid chemistry also was gradual in each case. The two patients, D. P. and J. S., without signs of meningeal irritation, but with characteristic spinal fluid changes, attained a normal spinal fluid within two months but the others required from four to six months to do so. The response of sugar, cells and protein in the two patients treated for the longest period of time, D. M. and P. S., is shown in Figure 1.

This roughly parallels the response observed in patients treated with streptomycin intramuscularly and intrathecally.

FIGURE I

Pattern of Response of Spinal fluid to Therapy with Streptomycin and Isonicotinic acid Hydrazide in Two Patients



The cerebrospinal fluid pressure returned to normal in all these patients but it did not show any fixed pattern of response. The fall to normal usually required between three and four months to occur. In none of these patients at any time during the course of therapy was there evidence of a block in the circulation of cerebrospinal fluid.

D. Bacteriological Response:

In three of the six children, J. S., L. L. and M. F., tubercle bacilli were isolated from the spinal fluid before the start of treatment. In only one case, L. L., was more than one positive culture for tubercle bacilli obtained, and this became negative within a period of three weeks after the initiation of therapy and has remained so. D. M., P. S. and D. P., who had had the longer periods of intramuscular streptomycin therapy before admission, did not show tubercle bacilli on repeated culture.

E. X-ray Film Changes:

Opportunity was afforded in the treatment of these patients to follow the course of their pulmonary tuberculosis under the influence of combined streptomycin and isoniazid therapy. The two who had miliary and associated tracheobronchial lymph node involvement had marked clearing of the pulmonary process within the first four months but there was slow retrogression of the lymph node foci. The three with combined pulmonary and lymph node involvement showed definite clearing of the parenchymal foci but little change in the lymph node components. Two of the latter, four to five months after initiation of therapy showed small areas suggestive of beginning calcification in the parenchymal lesions and one of them showed this change in the cervical lymph nodes also. The one patient with bilateral hilar lymph node enlargement without demonstrable pulmonary disease showed no change by serial roentgenograms.

F. *Toxic Manifestations:*

1) Hematopoietic System: There was no evidence in any of these patients of toxicity to the hematopoietic system during the prolonged usage of streptomycin and isoniazid. No significant eosinophilia was noted and there were no clinical evidences of increased bleeding tendency.

2) Urinalysis: Serial urine analyses did not reveal any evidences of marked renal toxicity to the therapeutic regimen. Each child had a faint trace of albumin on admission and intermittently during the course of treatment. There was no significant change in the cellular content of the urine. Occasional cylindroid and hyaline casts, and an occasional granular cast were seen, but no patient manifested any significant hematuria. The blood urea nitrogen was not altered in any case except once in J. S. without other signs or symptoms of renal toxicity.

3) Liver: Extensive liver function tests were not performed except for serial determinations of cephalin flocculation, thymol turbidity and the icteric index. Two infants, J. S. and D. P., developed, four months after the initiation of therapy, a 2+ cephalin flocculation test, and one, J. S.,

a thymol turbidity of 10.5 units. At no time did they have any evidence of hepatomegaly or jaundice, either clinical or biochemical and there were no correlative signs of liver disease. After the dose of INH was lowered to 5 mg. per kilo, thymol turbidity and cephalin flocculation gradually returned to normal.

4) Gastro-Intestinal Tract: Vomiting was a disturbing and severe complication in the early phases of treatment of all these patients. Most of them had relief of the vomiting when PAS was either stopped completely or the dosage reduced. Some did not respond to these measures and it may be that their vomiting was associated either with the use of streptomycin or was a result of the rise in the cerebrospinal fluid pressure, consequent to central nervous system inflammatory changes. Vomiting appeared to have no relation to the use of isoniazid orally or intramuscularly. In all cases after fluid replacement therapy and temporary cessation of oral feeding, the vomiting stopped and oral medications could be reinstituted.

5) Skin: Two infants developed transient erythematous maculopapular rashes, over the face, the upper trunk and the upper extremities. These disappeared within one or two days while both drugs were continued. No other cutaneous toxic manifestations were observed.

6) Central Nervous System: It was difficult to assess central nervous system toxicity in the presence of a disease with such overwhelming central nervous system manifestations as tuberculous meningitis. However, as the clinical state of the patient improved, frequent neurological examinations did not reveal any evidence of hyper-reflexia, muscular twitching or central nervous system stimulation described in earlier studies of isoniazid in adults.[27]

7) Cardiovascular System: There were no evidences at any time during the course of therapy of toxicity to the cardiovascular system from the use of these drugs. Electrocardiograms taken at the initiation of therapy and between four and six months after the use of isoniazid and streptomycin have revealed no evidences of myocardial toxicity.

Levels of Streptomycin and Isoniazid

Table II summarizes the data obtained on the simultaneous determinations of streptomycin and isoniazid in the plasma and spinal fluid at varying times after either an oral or intramuscular dose of isoniazid and intramuscular streptomycin. In the instances where two figures with an arrow between are recorded, these represent the range of values of a number of serial determinations. Two figures with comma represent two determinations. The plasma sample was taken no later than 10 minutes following the initiation of the lumbar tap. The streptomycin was given in the standard dose of 0.5 gm. intramuscularly once daily. The dose of isoniazid employed was the morning fraction of the total 10 mg. per kilogram daily dose of approximately 3.3 mg. per kilo. There was no significant difference in the levels obtained by oral or intramuscular administration of the drug. Plasma levels of isoniazid one and one-half hours after the dose varied from 1.5 to 6.7 mcg. per ml., from 0.5 to 5.8 mcg. per ml. at 5

TABLE II: Levels of Streptomycin and Isoniazid in Plasma and Spinal Fluid After I.M. or Oral Isoniazid and I.M. S.M.

	ONE AND A HALF HOURS AFTER DOSE				FIVE HOURS AFTER DOSE				TWELVE HOURS AFTER DOSE			
	I N H MCG/ML		S M MCG/ML		I N H MCG/ML		S M MCG/ML		I N H MCG/ML		S M MCG/ML	
	SP., FL.	PL.	SP., FL.	PL.	SP., FL.	PL.	SP., FL.	PL.	SP., FL.	PL.	SP., FL.	PL.
J.S.	1.5	1.4	<1.0	20+	3.1, 2.3	5.8	-, 0	-	2.0	1.0	-	-
M.F.	2.3	3.5	2.0	16.0	-	-	-	-	0.58	0.4	0.75	0.4
L.L.	3.8	6.1	20+	20+	0.5, 1.6	0.5, 2.2	-, 6.0	-, 16.0	2.3	0.46	4.0	0
D.M.	4.7	6.5	0	16.0	0.67 → 4.0	0.24 → 5.7	0.75 → 6.0	-, 20.0	1.2	0.65	0	0
P.S.	3.6	6.7	2.0	16.0	0.6 → 2.0	0.9 → 5.7	<1.0 → 8.0	-, 20.0	1.2	0.65	1.0	0

hours and from 0.4 to 1 mcg. per ml. at 12 hours. The spinal fluid levels indicated ready passage of the isoniazid molecule into the spinal fluid, varying from 1.5 to 4.7 mcg. per ml. at one and one-half hours, from 0.5 to 4 mcg. per ml. at five hours and from 0 to 1 mcg. per ml. at 12 hours after the dose.

The minimal inhibiting level of isoniazid in mcg. per ml. has been found to vary from .025 to .25 mcg. per ml. depending upon the medium employed.[6] Considerably more than the adequate tuberculostatic concentration of isoniazid was obtained both in the spinal fluid and in the plasma in all these children one and one-half to five hours after an oral or intramuscular dose. Even 12 hours after such a dose, the majority of patients showed more than the minimal tuberculostatic concentration.

The low streptomycin levels reported in the spinal fluid in Table II were obtained in the patients D. M., J. S. and P. S., who had normal spinal fluids at the time of these determinations.

Corroborative evidence was obtained indicating that isoniazid entered the spinal fluid in significant tuberculostatic concentrations in two cases. This was suggested by the following experiment: Dilutions of the spinal fluid from D. M. and P. S. were made in the range of 1:6 to 1:24 in Dubos medium. The dilutions and a control were then seeded with a recently isolated sensitive, virulent strain of human type tubercle bacilli. A small amount of growth was obtained in the 1:24 dilution but none in any of the other tubes. Controls without spinal fluid grew readily. At the time these tests were performed both spinal fluids had been normal for more than three months and the streptomycin levels were less than 1 mcg. per ml. These patients did not receive PAS during this time.

Discussion

Even a preliminary report on the clinical effectiveness of a therapeutic regimen ordinarily has little justification when limited to so small a number as six cases. However, the mortality rate in untreated tuberculous meningitis in infants is for all practical purposes 100 per cent within a relatively short period of time, rarely exceeding four to six weeks after the onset of the disease. The mortality of tuberculous meningitis in children when treated by the regimen of streptomycin intramuscularly and intrathecally aproaches an overall rate of from 30 to 50 per cent in the earlier reported series.[1,4,26,29] More recent results have shown a further reduction of mortality. Lincoln[31] reports survival of two out of three infants when treated in that fashion. In the recent Public Health Service study,[33] there were 26 survivors out of 93 cases, 12 with gross residua. Most of the deaths, even in the series with optimal results, occurred within the first six or seven months, with the peak occurring within the first to the third month.

The infants in the study here reported present a group of cases in which the expected mortality even with the accepted regimen, would have been considerably higher than the overall rate. All were less than two years of age on admission, two were comatose and two were semicomatose, two had associated miliary tuberculosis, and four had impairment of visual

and auditory acuity. Debre[26] in a recent review of 262 cases of tuberculous meningitis in children treated with streptomycin by the standard technique showed the overall mortality of 50 per cent was greatly increased by the following factors, among others: (1) age under 18 months; (2) the presence of miliary tuberculosis; (3) disturbance in the state of consciousness on admission. It can be seen that all of the infants in this series had at least two of these factors for increased mortality present. For these reasons, we consider that this group, though small, provides a sample of sufficiently high mortality potential that the anti-tuberculous activity of any drug or combination of drugs could be manifested early in the course of treatment.

From the standpoint of clinical, bacteriological and cerebrospinal chemical findings, the regimen of streptomycin intramuscularly in association with isoniazid without intrathecal medication appears to have a decided effect on the course of tuberculous meningitis when compared against the two standards of the prognosis of the untreated disease and the prognosis using the optimal previous technique of streptomycin intramuscularly and intrathecally in association with a sulphone. These children have been treated for periods ranging from four to 13 months. All six have shown marked and progressive improvement in their clinical state and in their cerebrospinal fluid chemistry and cytology. All have gained weight and none has shown evidences of bacteriological relapse. All have achieved an afebrile state.

Without a properly controlled parallel series of patients treated on the regimen of intramuscular streptomycin in association with intrathecal streptomycin and a sulfone, no definite comparison can be made with the suggested regimen of streptomycin and isoniazid without intrathecal streptomycin. However, it appears that this therapeutic regimen has resulted in a response at least equivalent to that which one might expect from a regimen of streptomycin intramuscularly and intrathecally. The disadvantages of intrathecal therapy would seem to be avoided. In addition, it would seem that isoniazid with its high rate of diffusibility into the cerebrospinal fluid makes a positive contribution to the antibiotic and chemotherapeutic regimen. The period of observation is far too short to warrant any conclusion about eventual outcome or relapse or about residual impairment of mental faculties.

Even at this early date it can be stated that this is not the ideal or the final answer to the treatment of tuberculous meningitis. In this series, as in others, it is quite apparent that the eventual outcome depends to a very great extent upon the degree of damage to the central nervous system present at the time of admission. The improvement of results in any therapeutic regimen, this one included, therefore, depends to a great extent as Lincoln and others have emphasized, upon the early recognition of this complication.[1,4,26]

Isoniazid alone is probably not sufficient in the treatment of tuberculous meningitis. This seems to be the indication in the few cases which were so treated by Clark, et al.[22] Therefore, although this group of cases would seem to indicate that isoniazid makes a definite contribution to the use

of streptomycin, it is probable that here as in other types of tuberculosis, isoniazid is most effective as an adjuvant to streptomycin therapy.

No conclusion in such a small number of cases can be drawn as to the effect of this regimen on the focal neurological lesions so often present in the child with tuberculous meningitis. In the children who have attained normal spinal fluid, these focal signs are absent. In the two children observed for a shorter time, the focal signs are becoming less marked. Also, four of these children had diminution in visual and auditory acuity on admission. There has been a slight but gradual improvement in these senses during the course of treatment.

There is a difference between the degree of response of the meningeal and cerebral irritative phenomena such as opisthotonos, muscular rigidity, convulsions, etc., and the focal signs of neurological involvement. The more general signs disappear more rapidly with prompt subsidence of convulsive seizures; there was a less prompt but early and progressive loss of muscular rigidity. Only considerably later was there a loss of the signs of focal damage.

It is apparent that isoniazid can be given in the relatively high dosage of 10 mg. per kilogram in this age group without serious toxic manifestations. The minor degrees of albuminuria may or may not have been related to the use of this drug. It is not unlikely that these slight traces of albumin in the urine represent a less specific effect related to the presence of systemic infection, pyrexia, streptomycin, etc. There was no significant change in the blood urea nitrogen value among these patients. Further observations are, of course, necessary to decide whether this urinary finding becomes more marked with the use of this therapeutic combination over longer periods of time. Although fatty degeneration of the liver has been noted in dogs given higher dosage levels of isoniazid,[15] there was no evidence in any of these infants of a significant degree of hepato-toxicity. The two patients, J. S. and D. P., who showed some slight abnormality of the cephalin flocculation test and one, J. S., of the thymol turbidity, did not show any other evidence of hepatic damage. Further, because hepatotoxicity was feared, the dosage level was cut in half in these children and following this after three months, the thymol turbidity and cephalin flocculation became normal. It cannot be definitely stated whether the abnormalities were due to liver damage or were the result of changes of the serum protein as a result of the general systemic tuberculous process, since these are the patients who had associated miliary tuberculosis. Further observations are being carried out to detect early signs of hepatic damage in the other patients, but to date none has been observed.

Observations of the effect of streptomycin and isoniazid used together on the accompanying primary tuberculosis of the lungs in these infants cannot be any more than tentative since the number of cases is small, and the period of observation is relatively short. The marked improvement in the two miliary cases over a period of four months is in keeping with the observation of Clark, et al.[22] The parenchymal infiltrates in all showed rather prompt and marked clearing, but the lymph node involvement was

much slower to respond. It was felt by the roentgenologist that the degree of improvement noted has been observed in other patients at this hospital with similar pulmonary lesions though usually not with this rapidity. These results suggest that the employment of streptomycin together with isoniazid might be worthy of further investigation in the treatment of children with primary tuberculosis, particularly if they are clinically ill and if they have extensive parenchymal lesions.

Our data on the levels of isoniazid in the plasma and spinal fluid indicate easy passage of this molecule into the cerebrospinal fluid, as was observed by others.[15,16] Many times the minimal tuberculostatic concentration was obtained in both the plasma and the spinal fluid at one and one-half hours, and five hours, after a dose of isoniazid, either by mouth or intramuscularly. Even 12 hours after such a dose there were from two to 10 times the inhibiting concentration in the spinal fluid. Thus, it appears safe to administer isoniazid during the day in divided doses without the necessity of giving this drug during the night.

It appears also, in the two cases in which the point was investigated, that the biochemical assay of isoniazid is paralleled by the bacteriologic assay, as noted by Elmendorf, et al.[16] Patients D. M. and P. S. had significant tuberculostatic activity of their spinal fluids at a time when the chemistry and cytology had been normal for more than three months and when the streptomycin levels were less than 1 mcg. per ml.

Because of the ready diffuisbility of the isoniazid molecule, both through inflamed and non-inflamed meninges, intrathecal isoniazid therapy may prove to be unnecessary in the majority of patients with tuberculous meningitis.

As reported by Lincoln[19] and others, we found that streptomycin entered the spinal fluid only when there was evidence of meningeal inflammation. As the cytology and chemistry of the spinal fluid showed improvement, the streptomycin level fell to zero or negligible values.

Furthermore, it has been shown that streptomycin intramuscularly without intrathecal use is of limited value in the treatment of tuberculous meningitis.[29,30] It is not to be expected that the results observed could have been obtained by the use of intramuscular streptomycin alone. It seems rather that the use of streptomycin and isoniazid together produces a clinical response in tuberculous meningitis which neither of these agents is capable of producing alone. This is in keeping with the recently reported observations of Mackaness on the survival rate of M tuberculosis H37Rv in vitro and in mammalian macrophages in which activity was produced by the combined use of streptomycin and isoniazid.[32] Another advantage in the use of combined antituberculous agents is the delaying of bacterial resistance. Early indications are that this may be true in the case of streptomycin and isoniazid[18,19] (our own laboratory).

It is felt that prolonged treatment with streptomycin as well as isoniazid is necessary, even though streptomycin does not enter the spinal fluid in appreciable concentration when the evidences of meningeal inflammation have subsided. This is advisable not only to forestall the emergence of

bacterial resistance but also to obtain the effect of both drugs on bacilli which may still be present in the initial forms or in meningeal lesions from which relapse may occur. Dubos has re-emphasized the importance of this point[28] as have most of the clinical authorities. The observations of Mackaness and Smith[32] are pertinent in this regard also because they indicate that to obtain a combined effect of streptomycin and isoniazid, a relatively higher concentration of streptomycin must be maintained since this substance does not enter the cell to any great degree.

All these children are still under treatment at the time of this report. We intend to continue combined treatment for a period of one year This would seem to be justifiable in view of the known proclivity of the disease to relapse and in view of the experience in the larger series of patients indicating better results with longer periods of therapy.

This series is too small to justify any statements on the effect of this therapeutic regimen in forestalling the appearance of cerebrospinal fluid block. However, none has occurred during the period of observation. This may be related to the absence of chemical irritation of streptomycin injected intrathecally as well as the greater diffusibility of isoniazid into tissue fluids and into cells so that living bacilli may be acted upon even when engulfed by macrophages, epithelioid cells or even fibrin.

ADDENDUM

Since we used PAS intermittently and irregularly during the acute phases of the disease, we were not able to evaluate its contribution to the therapeutic regimen in this series. Our clinical impression is that it is not essential to the therapeutic efficacy of the regimen. We do feel though that when it can be tolerated, it should be used for whatever tuberculostatic effect it may have. We would like to suggest its use during convalescence along with isoniazid.

We have used promizole only on two patients in late convalescence and do not feel justified in making any statements concerning its value. Further investigation of the value of PAS or promizole in addition to the basic streptomycin-isonicotinic acid hydrazide combination is justified.

D.M.: Progressive clinical improvement. Pulls himself up and walks around the crib, holding on to the sides. Recent spinal fluid values normal. Markedly diminished hearing and vision. Extreme lack of coordination. SM stopped July 14, 1953. Continues on IAH and PAS. To be discharged soon to continue drugs at home.

P.S.: Slow, progressive clinical improvement. Spinal fluid normal. SM stopped July 17, 1953. IAH continued and Promizole later added to regimen in place of PAS.

J.S.: Continued clinical improvement. Spinal fluid normal. SM stopped July 2, 1953. To continue IAH and PAS at home.

L.L.: Progressive clinical improvement. SM stopped November 1, 1953. Discharged November 1, 1953. To continue IAH and PAS at home. Spinal fluid normal

M.F.: Progressive clinical improvement. SM and IAH continued. Promizole recently added to regimen in place of PAS. Spinal fluid normal.

D.P.: Clinically well. Growing and developing normally. Spinal fluid normal. Normal intelligence. Continues SM, IAH and PAS. Would be ready for discharge to good home conditions which she does not have, and will be retained here.

SUMMARY

1) Six infants, ranging in age from seven to 21 months, have been treated for tuberculous meningitis on a regimen of streptomycin and isoniazid 10 mg. per kilogram by mouth or by intramuscular injection. All were acutely ill on admission; four were comatose or semi-comatose and two had accompanying miliary tuberculosis.

2) These patients have been treated for periods ranging from four to 13 months. All have shown marked to moderate clinical improvement. The four treated for the longest periods of time have achieved a normal cerebrospinal fluid and have lost all evidence of meningeal irritation and of focal neurological lesions which were present on admission. None has shown any progression of disease and all have shown repeatedly negative spinal fluid cultures for tubercle bacilli and none has had a bacteriological relapse. None has developed cerebrospinal fluid block.

3) There was no evidence of any serious toxic manifestation as a result of the combined use of these drugs for prolonged periods of time. Transient slight albuminuria was frequently seen. Transient maculopapular rashes were seen in two cases and a disturbance of cephalin flocculation in two cases and thymol turbidity in one case. Despite continued therapy, these abnormalities have not persisted or progressed.

4) Significant levels of isoniazid were detected in the spinal fluid one and one-half hours, five hours and even 12 hours after either an oral or intramuscular dose of drug.

5) All these children had associated tuberculosis of the lungs. The patients with associated miliary tuberculosis of the lungs have shown marked improvement in the pulmonary and meningeal manifestations of their disease. Two other patients with parenchymal infiltration have shown marked to moderate improvement by serial roentgenographic examination.

6) It is felt, considering the mortality potential in this age group and with these clinical findings, that a definite favorable change in the course of tuberculous meningitis has been obtained. It is the clinical impression that these results are at least similar to what one would have expected with the regimen employing streptomycin systemically as well as intrathecally in association with or without a sulfone. The disadvantages of intrathecal therapy appear to have been avoided without a loss of bacteriostatic effect. Prolonged therapy on this regimen for a minimum of one year is suggested.

7) Further study of the use of streptomycin in combination with isoniazid in treatment of tuberculous meningitis would appear to be indicated.

The authors wish to express their gratitude to Miss Lillian Whitney, R.N., and the staff of the Children's Division for energetic and enthusiastic nursing care and to Dr. Edmund H. Kerper, for assistance in the interpreting of roentgenograms.

RESUMEN

1) Se trataron seis niños de 7 a 21 meses de edad con meningitis tuberculosa por medio de estreptomicina: ½ gmo. diario e isoniacida: 10 mg. por kilo, por vía oral o intramuscular. Todos se encontraban severamente

enfermos a su ingreso; cuatro comatosos, o semicomatosos y dos, tenían además, tuberculosis miliar.

2) Estos enfermos se trataron por periodos de 4 a 13 meses. Todos tuvieron mejoría clínica moderada o marcada. Los cuatro tratados por periodo más largo, han llegado a tener líquido cerebroespinal normal, y en ellos, ha desaparecido toda evidencia de irritación meníngea así como de las lesiones neurológicas focales que presentaron a su ingreso. Ninguno ha mostrado un empeoramiento de la enfermedad y ninguno ha tenido recaída bacteriológica. Ninguno ha tenido bloqueo del líquido cerebroespinal.

3) No hay evidencia de manifestación tóxica alguna como resultado de la combinación de estas drogas por periodos largos de tiempo. Se ha visto albuminaria frecuente transitoria. Manchas cutáneas maculopapulares se vieron en dos casos y alteraciones de la cefalín floculación en dos casos y turbidez al timol en uno. A pesar de la continuada terapéutica, estas alteraciones, no persistieron ni progresaron.

4) Se encontraron tenores significantes de isoniacida, en el líquido espinal una hora y una y media horas, así como cinco y aún 12 horas después de la administración oral o intramuscular de la droga.

5) Los enfermos con miliar asociada en los pulmones, mostraron marcada mejoría en las manifestaciones meníngeas y pulmonares de la enfermedad. Otros dos enfermos con infiltración parenquimatosa, mostraron mejoría marcada según la serie radiológica.

6) Se cree, considerando el elevado potencial de mortalidad de este padecimiento en esta edad, que se ha obtenido un cambio definido favorable en la evolución de la meningitis tuberculosa. La impresión clínica, es que estos resultados cuando menos, son similares a los que se esperarían empleando estreptomicina parenteral al mismo tiempo que intratecal, con asociación de una sulfona. Las desventajas de la terapéutica intratecal, parecen haber sido evitadas sin una pérdida de efecto bateriostático. Se sugiere el tratamiento prolongado con este régimen por un mínimo de un año.

7) Parecen indicados ulteriores estudios sobre el uso de la estreptomicina combinada con la isoniacida en la meningitis tuberculosa.

RESUME

1) Six enfants âgés de 7 à 21 mois atteints de tuberculose méningée, ont été traités par 50 cgr. de streptomycine et 10 mmgr. d'isoniazide par kilogramme, soit par voie buccale, soit par injection intramusculaire. Tous étaient en période aigue lors de leur admission, quatre étaient comateux ou semi-comateux et deux avaient une tuberculose miliaire associée.

2) Ces malades ont été traités pendant un laps de temps allant de quatre à treize mois. Tous ont montré une amélioration clinique soit très nette, soit modérée. Les quatre enfants qui ont été traités pendant la temps le plus long ont fini par avoir un liquide céphalo-rachidien normal, et ne présentent plus aucun signe d'irritation méningée, ou de lésions neurologiques localisées, telles qu'ils en avaient au moment de leur admission. Chez aucun d'entre eux, l'affection n'a continué à évoluer, tous ont actuel-

lement un liquide céphalo-rachidien dépourvu de bacilles, même à la culture, et il n'y à eu aucune rechute bactériologique. Aucun de ces malades n'a eu de blocage du liquide céphalo-rachidien.

3) Les auteurs n'ont constaté aucune manifestation toxique sérieuse, à la suite de l'utilisation de ces drogues associées pendant une période de temps prolongé. Une légère albuminurie transitoire à été notée souvent. Dans deux cas, apparurent des rashs de type maculopapuleux et transitoire. Deux malades eurent un trouble de la floculation à la céphaline, et l'un une opacification au thymol. Ces anomalies n'ont ni persisté, ni progressé malgré la continuation du traitement.

4) Des taux importants d'isoniazide furent constatés dans le liquide céphalo-rachidien, une heure, une heure et demie, cinq heures et même douze heures après administration de ce produit par voie bucale ou intramusculaire.

5) Tous ces enfants étaient atteints de tuberculose pulmonaire associée. Les malades qui avaient une atteinte miliaire des poumons associée montrèrent une amélioration notable à la fois des manifestations pulmonaires et méningées. Chez deux autres malades atteints d'infiltration parenchymateuse, des radiographies en séries ont montré une amélioration marquée ou modérée.

6) Les auteurs considèrent, étant donné la mortalité habituelle à l'âge des malades qu'ils ont étudiés et avec les symptômes qu'il ont eus, qu'ils ont obtenus une modification tout à fait favorable de l'évolution de la méningite tuberculeuse. Ces résultats donnent l'impression qu'ils sont au moins semblables à ce que l'on pourrait attendre d'un traitement systématique à la streptomycine intra-rachidienne associée ou non aux sulfones. Les inconvénients du traitement intra-rachidien semblent avoir été évités sans que l'on ait perdu une part de l'action bactériostatique. Les auteurs proposent que le traitement qu'ils emploient soit prolongé au minimum pendant une année.

7) Il semble indiqué de continuer à étudier l'utilisation combinée streptomycine-isoniazide dans le traitement de la tuberculose méningée.

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Tryptar in Intrathoracic Disease*

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Tryptar is a brand of highly purified crystalline trypsin prepared from mammalian pancreas glands. The enzyme is stable indefinitely at room temperature but when placed in solution approximately 50 per cent of the proteolytic activity is dissipated within four hours. For this reason, tryptar solutions should be prepared freshly each time before use.

Tryptar is effective over a pH range of 5 to 8, exhibiting its greatest activity at about pH of 7. It has a broad spectrum of hydrolytic activity on proteins degrading them to small polypeptides and some amino acids. There is a considerable differential in the destruction of various groups of proteins by tryptar since denatured protein and flat chain molecules, such as fibrin and fibrinogen, are hydrolyzed much more rapidly than other proteins.

Tryptar is not active upon and does not harm living tissues since it has shown that trypsin does not penetrate the viable cell membrane. In addition, each cell contains a specific trypsin inhibitor which protects the cell from proteolytic action of the enzyme. Serum also contains specific and non-specific trypsin inhibitors which counter the effects of tryptar.

Signs of sensitization or clinical antigenicity to tryptar have not been observed. The enzyme may be safely used over prolonged periods or recurrently after long intervals.

Tryptar is a useful agent to the surgeon to remove intrapleural deposits of fibrin.[1] The following reports of cases show the indications, methods, limitations and results obtained from its use for these purposes.

Report of Cases

Case 1: A 25 year old Negro man, admitted to the hospital on April 6, 1952, had incurred a stab wound of the left side of the chest on April 5, 1952. He had been admitted first to another hospital then transferred to this hospital. The roentgenogram of the chest on admission showed fluid in the left pleural cavity (Figure 1). Intercostal closed catheter drainage, to which suction of about −20 cm. of water was connected, was provided on April 6. Tryptar,† 250,000 Armour units in 20 cc. of Sorenson's Phosphate Buffer Solution was injected through the catheter twice a day from April 7 through April 14. The catheter was clamped for four hours to permit digestion and then suction was reapplied. He was given penicillin and cholormycetin. He also received benedryl in doses of 0.1 gram for the first dose and then 0.05 gram four times a day. The roentgenogram of April 10 (Figure 2) showed little change. The quantity of aspirated blood decreased and the fluid

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†The Tryptar was supplied by The Armour Laboratories.

became serous so that it was possible to remove the catheter on April 14. A considerable diminution in the quantity of fluid in the pleural cavity was noted on the roentgenogram of April 17 (Figure 3). He was discharged from the hospital on April 21. On May 21, he stated that he was asymptomatic and was working at his usual occupation. The roentgenogram of May 21 showed slight thickening of the pleura and obliteration of the costophrenic angle on the left side (Figure 4).

Case 2: A 26 year old Negro man, admitted to the hospital on May 2, 1952 had incurred a stab wound of the right side of the chest on the same day. He had been admitted previously to another hospital where about 500 cc. of blood had been aspirated from the right pleural cavity. He had been transferred to this hospital

FIGURE 1 FIGURE 2

Figure 1: Left hemothorax on April 6, 1952.—*Figure 2:* Left hemothorax after intercostal closed catheter drainage and treatment with Tryptar on April 10, 1952.

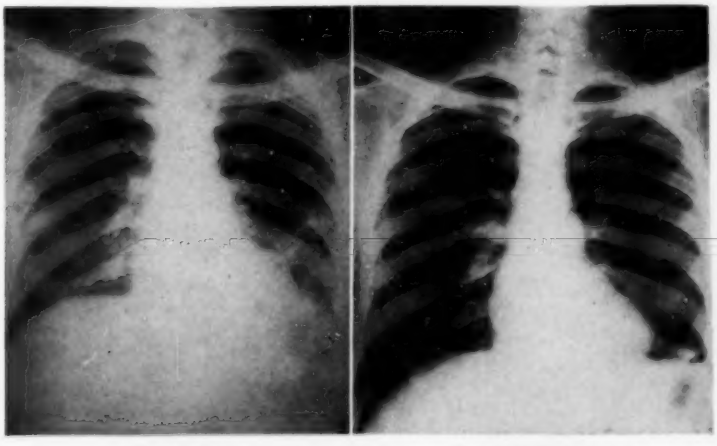

FIGURE 3 FIGURE 4

Figure 3: Left hemothorax on April 17. Catheter has been removed.
Figure 4: Roentgenogram of chest on May 21.

for further care. The roentgenogram of the chest on May 2 showed a moderate amount of fluid in the right pleural space. Upon aspiration, this was found to be sanguineous. Intercostal closed catheter drainage with suction of about −20 cm. of water was provided on May 2, with about 300 cc. of sanguineous fluid being removed at the time of operation. The patient was given penicillin and benedryl. Tryptar, 200,000 Armour units in 25 cc. of Sorenson's phosphate buffer solution, was injected through the catheter twice a day from May 3 through May 7. The catheter was clamped for three hours to permit digestion after which suction was re-established. The quantity of sanguineous fluid had decreased and the fluid had become serous, so the catheter was removed on May 12. The roentgenogram of

FIGURE 5

FIGURE 6

Figure 5: Left empyema on February 28, 1952.—*Figure 6:* Left loculated collection of fluid with overlying air on March 21, 1952.

FIGURE 7

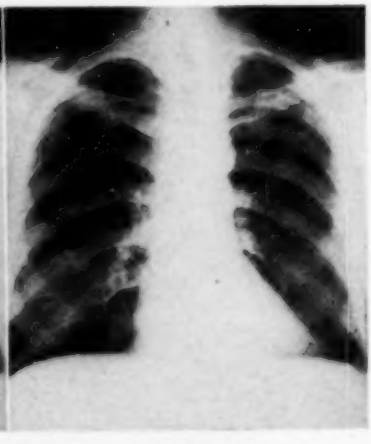

FIGURE 8

Figure 7: Roentgenogram showing diminution of fluid in left pleural cavity on April 5, 1952.—*Figure 8:* Roentgenogram of chest on April 24, 1952.

May 12 showed a decreased amount of fluid while that of May 20 showed some thickening of the pleura in the lower part of the chest with blunting of the costophrenic angle. He was discharged from the hospital on May 20. On June 20, he stated that he was asymptomatic. The roentgenogram of June 20 showed some resolution of the thickening of the pleura.

Case 3: A 46 year old white man was admitted to the surgical service on February 8, 1952 for the treatment of pain in the back and over the left ilium for about 17 years which was due to rheumatoid arthritis. He denied having symptoms referable to the lungs although the physical examination indicated that pneumonitis and pleural effusion were present on the left side. The roentgenogram of the chest made on February 9 showed left pneumonitis and pleural effusion. About 1,200 cc. of fluid were aspirated from the pleural cavity on February 16. Aerobic and anaerobic cultures of the fluid were sterile. Acid-fast bacilli were not found by smear or culture. Repeated examinations of the sputum and gastric washings were negative for acid-fast bacilli. He was given penicillin, aureomycin and terramycin at various times during the stay in the hospital. He was transferred to the medical service for further care. The effusion (Figure 5), however, subsequently became purulent and about 50 cc. of foul-smelling green pus were aspirated from the pleural cavity on March 3. A Streptococcus anaerobius and a microaerophilic Streptococcus viridans were cultured from the pus. He was transferred back to the surgical service and an intercostal closed catheter drainage with suction of about −20 cm. of water was provided on March 3. He was given benedryl. Tryptar, 200,000 Armour units in 20 cc. of Sorenson's phosphate buffer solution, was injected through the catheter twice a day from March 3 through March 7. The catheter was clamped for four hours after the injection of tryptar to permit digestion after which the suction was re-established. About 1,500 cc. of pus were aspirated during the first 24 hours. Repeated roentgenograms showed progressive resolution and when the fluid became serous on March 10, the catheter was removed. A loculated collection of fluid with overlying air was noted on March 21 (Figure 6) and this was thought to be the result of bronchopleural fistula. Intercostal closed catheter drainage with suction was re-established on March 21. Tryptar was given in a similar manner from March 22 through April 1. The suction

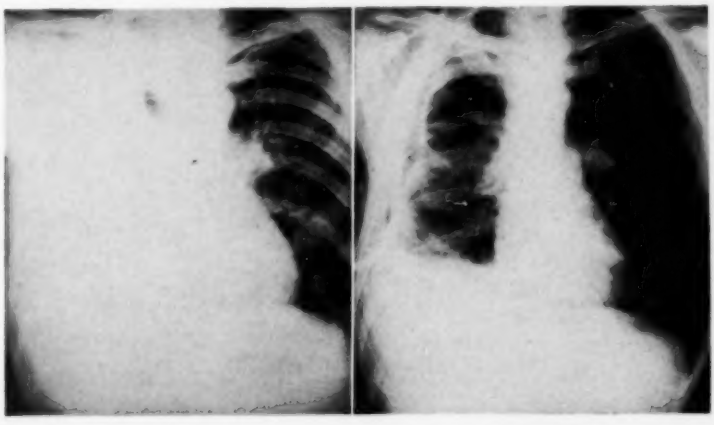

FIGURE 9 FIGURE 10

Figure 9: Right pleural effusion on March 15, 1952.—*Figure 10:* Right empyema after intercostal closed catheter drainage and treatment with Tryptar on March 26, 1952.

was discontinued and the catheter cut at the chest wall on April 5. The roentgenogram on April 5 showed considerable diminution in the quantity of the fluid (Figure 7). The catheter was removed on April 7. An excellent response was obtained. On April 10, roentgenograms showed some thickening of the pleura. The wound healed and the patient was transferred to the medical service for further care of the rheumatoid arthritis. The roentgenogram of April 24 showed only a blunting of the costophrenic sinus (Figure 8). He was discharged from the hospital on May 8.

Case 4: A 31 year old white man, admitted to the medical service on March 15, 1952 with a history of having a respiratory infection for three weeks, was found to have pneumonitis with pleural effusion on the right side (Figure 9). Aureomycin, penicillin and terramycin were given at various periods during the stay in the hospital. Pus, from which pneumococci were cultured, was aspirated from the pleural cavity on March 18. He was transferred to the surgical service on March 18 and a closed intercostal catheter drainage, with suction of about —20 cm. of water, was provided on the same day. He was given benedryl. Tryptar, 200,000 Armour units in 30 cc. of Sorenson's phosphate buffer solution was injected through the catheter three times a day from March 18 through April 11. The dose was changed to 250,000 units in 20 cc. once a day from April 12 through April 25. The catheter was clamped for four hours after each injection to permit digestion after which the suction was re-established. About 1,800 cc. of pus were aspirated from the pleural cavity in the first 24 hours. A bronchopleural fistula was noted on March 25. Considerable improvement was seen on the roentgenogram of March 26 (Figure 10) with slight additional progress being noted on April 5 (Figure 11). Repeated roentgenograms showed progressive improvement so that it was possible to remove the catheter on April 26. A peripheral zone of increased density over the right lung with obliteration of the right costophrenic sinus was seen on the roentgenogram of May 6 (Figure 12). He was discharged from the hospital on May 9.

Case 5: A 34 year old Negro man was admitted to the medical service on May 21, 1952 with pain in the right side of the thorax. A diagnosis of bronchopneumonia and pleurisy with effusion on the right side was made. He was treated with aureo-

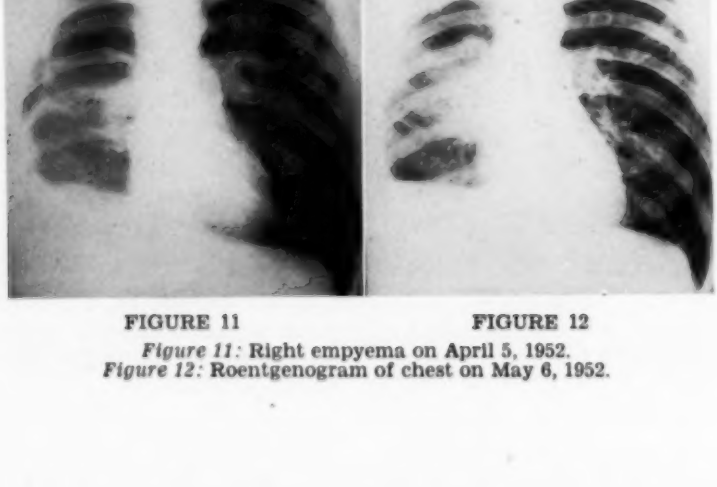

FIGURE 11 FIGURE 12

Figure 11: Right empyema on April 5, 1952.
Figure 12: Roentgenogram of chest on May 6, 1952.

mycin. About 250 cc. of dark amber fluid were aspirated from the right pleural cavity on May 27. The fluid was sterile in aerobic and anerobic culture. The temperature, however, continued to be moderately elevated. He was subsequently seen in consultation by the surgical service. Aspiration of a loculated area in the right pleural cavity produced about 3 cc. of foul-smelling pus, cultures of which were sterile, aerobically and anaerobically. He was transferred to the surgical service. Intercostal closed catheter drainage with suction of about −20 cm. of water was provided on June 23. At the time of operation about 40 cc. of malodorous pus was aspirated. He received penicillin at this time. Tryptar, 200,000 Armour units in 15 cc. of Sorenson's phosphate buffer solution, was injected through the catheter twice a day from June 24 through June 30. The catheter was clamped for about three hours after injection to permit digestion and then suction was re-established. Benedryl was given during this period. During the treatment with Tryptar, the pus became much thinner. The catheter was removed on July 6. He was discharged from the hospital on July 14. At a follow-up examination on August 14, he was asymptomatic. The roentgenogram of August 14 showed only an area of thickening of the pleura in the right cardiophrenic angle.

Case 6: A 35 year old white man, admitted to the medical service on December 31, 1951 had had a sudden onset of pain in the left side of the chest about one week previously. It was associated with a non-productive cough and fever of an undetermined height. The patient had incurred a gunshot wound of the left side of the chest in 1943. The injury was complicated by empyema which necessitated performance of several operations. The temperature was elevated to 101 degrees F. The roentgenogram of January 3, 1952 (Figure 13) showed left pleural effusion. On January 4, pus was noted draining from the mid-portion of the scar on the left side of the chest wall. Staphylococcus aureus was cultured. He was seen in consultation by the surgical service on January 4 when the diagnosis of an empyema necessitans was apparent. He was transferred to the surgical service and an unroofing of the empyema cavity was done on January 4. About 200 cc. of thick pus were evacuated. Two number 18 French catheters were placed into the base of the wound which was packed open with nylon gauze. Suction of about −20 cm. of water was applied to the catheters in turn. He was given penicillin and

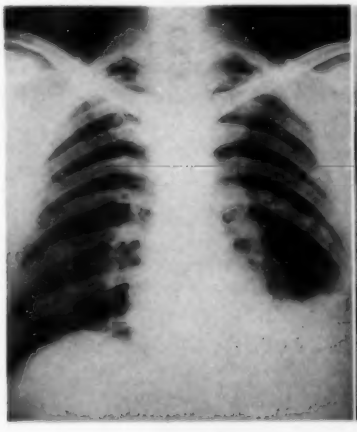

FIGURE 13

FIGURE 14

Figure 13: Left pleural effusion on January 3, 1952.
Figure 14: Wound on January 10, 1952.

FIGURE 15

FIGURE 16

FIGURE 17

Figure 15: Roentgenogram of chest on January 14, 1952.
Figure 16: Wound on January 15, 1952.
Figure 17: Roentgenogram of chest on January 28, 1952.

sulfadiazine at various times during the stay in the hospital. Tryptar, 100,000 Armour units in 10 cc. of Sorenson's phosphate buffer solution was injected through one of the catheters daily from January 5 through January 8. The catheters were clamped for four hours to permit digestion and then the suction was re-established. The pack and catheters were removed from the wound on January 8. Tryptar powder was blown into the wound (Figure 14) to form a fine film by a DeVilbiss blower once daily from January 9 through January 15. The roentgenogram of January 14 showed considerable improvement (Figure 15). The wound (Figure 16) became clean. Partial thoracoplasty and closure of the wound was done on January 16. A number 20 French catheter was placed into the base of the wound. Tryptar, 33,000 Armour units in 5 cc. of Sorenson's phosphate buffer solution was injected through the catheters into the wound every six hours from

FIGURE 18

FIGURE 19

Figure 18: Wound on February 19, 1952.
Figure 19: Roentgenogram of chest on May 2, 1952.

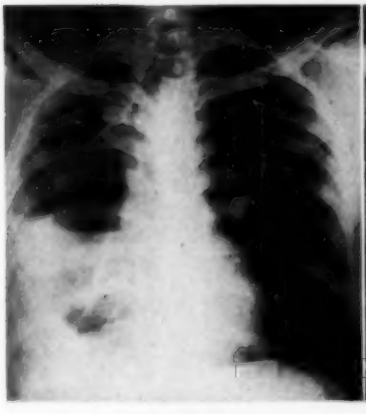

FIGURE 20

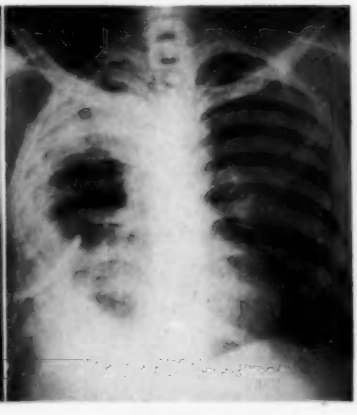

FIGURE 21

Figure 20: Collapse of right lung and pleural effusion on December 19, 1951.
Figure 21: Roentgenogram of chest on January 23, 1952.

FIGURE 22 FIGURE 23 FIGURE 24

Figure 22: Roentgenogram of chest on January 29, 1952.
Figure 23: Roentgenogram of chest on February 11, 1952.
Figure 24: Roentgenogram of Chest on June 12, 1952.

January 17 through January 24. The catheter was clamped for four hours to permit digestion and then the suction was re-established. He was given benedryl. During this period 20 cc. to 50 cc. of sanguinoserous fluid were aspirated from the wound daily. The catheter was removed from the wound on January 24 when the main portion was healed. The roentgenogram of January 28 (Figure 17) showed improvement. The tract of the catheter was healed on February 14. The wound (Figure 18) looked good on February 19. He was discharged from the hospital on February 19. On May 2, he stated that he was well and was working full-time as a truck driver. The roentgenogram of May 2 (Figure 19) showed a slight collapse of the lateral wall on the left side and clear lungs.

Case 7: A 25 year old white man, admitted to the hospital on May 4, 1952, had had bronchiectasis for seven years. Bronchography showed dilatation and sacculation of the lingula of the upper lobe and all of the basilar segments of the lower lobe of the left lung and minimal changes in the anterior segment of the right lung. On May 28, the lingula and the basilar segments were resected. Intercostal closed catheter drainage with suction of about −20 cm. of water was provided. However, hemothorax formed postoperatively. Benedryl was administered. Tryptar, 200,000 Armour units in 25 cc. of Sorenson's phosphate buffer solution was injected through the catheter into the pleural space twice a day for 11 days. The catheter was clamped for three hours after each injection after which suction was re-established. Large amounts of sanguineous fluid were aspirated from the pleural cavity. The roentgenograms showed progressive improvement. The catheter was removed on June 18. The temperature however, became elevated and foul-smelling pus was aspirated from the pleural cavity on June 24. Escherichia coli and an unidentified micrococcus were cultured from the pus. Intercostal closed catheter drainage with suction was re-established on June 25. Tryptar was injected into the pleural cavity in a similar manner from June 26 through June 30 when the injections were discontinued due to a lack of the agent. The injections of tryptar were resumed from July 10 through July 14. The infection, however, was not controlled. The pocket was unroofed by resection of the overlying rib on July 15. About 30 cc. of pus were evacuated from the loculation. A small bronchopleural fistula was found at the medial part of the wound. The wound was packed open with nylon into which plain gauze was placed. Tryptar was blown into the wound to form a fine film by a DeVilbiss blower from July 17 through August 4. The cavity gradually became clean. The wound was closed on August 5. The pocket then measured 6 by 3 by 3 cm. and the bronchopleural fistula was still present. The overlying ribs were resected and the intercostal muscles sutured in such a manner as to occlude the bronchopleural fistula. Two number 20 French catheters were inserted into the depths of the wound for air-vent suction and brought out through its anterior end. Flaps of muscle were developed and the pocket filled. Suction of about −20 cm. of water was applied to the catheters which were removed on August 11. The wound healed well. He was discharged from the hospital on September 9 to return for observation for the bronchiectasis in the upper lobe of the right lung. On October 9, he stated that he did not have dyspnea. Very little expectoration was noted although occasionally the sputum was tinged with blood. He had gained 8 pounds. The roentgenogram of October 9 showed some clouding of the lower third of the left lung field. On November 21, he stated that he felt well. He had a little expectoration which was not tinged with blood. The bronchogram of November 21 showed minimal bronchiectasis of the anterior segment of the upper lobe of the right lung.

Case 8: A 56 year old white man, admitted to the hospital on September 14, 1951, had right pneumonectomy for bronchogenic carcinoma on October 9. A bronchopleural fistula was noted on December 10. An intercostal closed catheter drainage, to which suction of about 20 cm. of water was applied, was provided on December

10. A large amount of pus was obtained. Although his general condition improved, the fistula persisted. Suction was discontinued and a short segment of catheter to act as a drain was inserted into the pleural cavity. He was discharged from the hospital to the care of his local physician on February 9, 1952. On his return to the hospital on March 18, the fistula was still present. A catheter was inserted and tryptar, 200,000 Armour units in 5 cc. of Sorenson's phosphate buffer solution was injected once a day from March 23 through April 9. He was postured for two hours to retain the solution. The pus decreased in amount by 50 per cent, became less viscid and lost a part of the foul odor. Evidence of a spread of the infection into the left lung was not seen. On April 11, first stage anterior thoracoplasty was done. He was given penicillin. The drainage from the catheter decreased in amount. The operative wound healed. On May 1, second stage posterior thoracoplasty was done. The fistula closed on May 2. The operative wound healed. Proteus vulgaris was cultured from the pus at the site of the drainage. The tract for the catheter healed on May 17. He was discharged from the hospital on May 23, but was admitted to another hospital on June 14 critically ill with dyspnea, cyanosis and jaundice. He died shortly after admission with the autopsy showing pus in the right pleural space, acute and chronic myocarditis and chronic passive congestion of the liver, spleen and kidneys with toxic degeneration.

Case 9: A 63 year old white man was admitted to the medical service on January 28, 1952 for atelectasis of the middle part of the right lung. A diagnosis of tuberculosis of the peritoneum had been made elsewhere previously with enlarged liver and spleen being found at operation. In March 1952, he developed pleural effusion on the right side. Repeated examinations of sputum, gastric washings and fluid from the right pleural cavity were negative for acid-fast bacilli. He was transferred to the surgical service for observation, investigation and further treatment of his disease. Intercostal closed catheter drainage with suction was established on May 23. Tryptar, 200,000 Armour units in 30 cc. of Sorenson's phosphate buffer solution was injected into the right pleural cavity daily from May 23 to June 3. Large amounts of sanguineous fluid were aspirated from the pleural cavity but only moderate clearing occurred. The catheter was removed on June 3. Sanguineous fluid was thereafter obtained by aspiration at irregular intervals. The leukocyte count which was 14,100 per cmm. on June 5 rose to 43,200 per cm. on July 1. Purulent fluid was subsequently aspirated from the right pleural cavity. Right thoracotomy to obtain pleura or lung for biopsy and to provide drainage was done on July 22. A moderate amount of necrotic debris and clotted blood was present. The lower lobe was decorticated. The underlying lung was free of disease. Intercostal closed catheter drainage was provided. Biopsy showed tuberculous pleurisy and occasional acid-fast bacilli were demonstrated. Streptomycin and hydrazid were started but he did poorly. The leukocyte count rose to 260,200 per cmm. and then to 302,500 on August 30. Although it was strongly suspected during the long period of illness that he had chronic myeloid leukemia, it was the feeling of the hematologist that the elevated leukocyte count was due to a leukemoid reaction. He died on August 30. Tuberculous empyema with secondary infection of the right side, extensive tuberculosis of the lymph nodes and chronic myeloid leukemia were found at autopsy.

Case 10: A 26 year old Negro man had resection of the upper lobe and the superior segment of the lower lobe of the right lung and thoracoplasty done for tuberculosis on May 29, 1952. One catheter was brought out in the first intercostal space in the anterior axillary line and a second in the eighth intercostal space in the posterior axillary line. A water seal was provided for the anterior catheter while suction of about −20 cm. of water was applied to the posterior catheter. Due to excessive drainage of sanguineous fluid from the chest, the suction was discontinued in a short time after operation. About 1,300 cc. of sanguineous fluid

were aspirated from the chest during the first 24 hours after operation. Since the posterior catheter was not functioning, it was removed on May 31. Aspiration of the pleural space produced only a few cc. of blood. The roentgenogram of June 2 showed a diffuse density over the right side and it was apparent that clotted hemothorax was present. The anterior catheter was removed and closed intercostal catheter drainage through the fifth space to which suction of about −20 cm. was attached, was provided on June 2. He was given benedryl. Tryptar, 200,000 Armour units in 25 cc. of Sorenson's phosphate buffer solution, were injected through the catheter four times a day from June 3 through June 7. The catheter was clamped for four hours after injection to permit digestion after which suction was re-established. About 375 cc. of sanguineous fluid were aspirated during the first 24 hours after treatment with tryptar was started and about 800 cc. during the second. Additional fluid was not obtained. The catheter was removed on June 10. Bronchoscopy with aspiration of a moderate amount of secretion was done on June 5 and repeated on June 9 when only a small amount of mucoid secretion was obtained. Tryptar, 50,000 Armour units in 10 cc. of Sorenson's phosphate buffer solution, was put into the right main bronchus through a catheter passed through the bronchoscope. Repeated roentgenograms showed progressive resolution of the effusion and on June 16, the lower lobe was considerably expanded. He was transferred to the medical service for further care on July 7. On July 30, the roentgenogram showed further expansion of the lower lobe with considerable resolution of the effusion. On November 10, the roentgenogram showed good aeration of the remaining portions of the right lung and only minimal thickening of the pleura.

Case 11: A 34 year old Negro man, admitted to the surgical service on December 17, 1951 was found to have tuberculosis of the right lung in August 1944. He was on bed rest until June 1945 when pneumothorax was established and continued until August 1949. At the time of re-examination in November 1950, hydropneumothorax was present. Sanguineous fluid was aspirated from the pleural cavity in January 1951 and during the next three months. The sputum had been negative for acid-fast bacilli since 1945. He was referred to the hospital for decortication of the right lung. Repeated examinations of the sputum and gastric washings were negative for acid-fast bacilli. The roentgenograms of the chest showed 50 per cent collapse of the right lung with a fluid level at the seventh rib posteriorly (Figure 20). Closed intercostal catheter drainage was provided on January 2, 1952. Five injections of tryptar, 200,000 Armour units, in 20 cc. of Sorenson's phosphate buffer solution were given at irregular intervals between January 2 and January 17. Benedryl was administered. He also received penicillin and chloromycetin. The fluid in the pleural cavity was serous at first. During the treatment with tryptar, large amounts of fibrinous material were noted in the aspirated fluid but blood was never seen. The temperature became elevated to as high as 104 degrees F. during this period. The lung, however, did not expand (Figures 21 and 22) and decortication was done on February 7. A moderate amount of fibrinous material was still present in the pleural cavity although the pleural space was clean. The peel was about 0.6 cm. thick in some places. Intercostal closed catheter drainage with suction of about −20 cm. of water was provided. The roentgenogram showed good progress (Figure 23) and the catheter was removed on February 18. He was discharged on March 11. On June 12, he stated that his activity was normal although he had not yet returned to work. The roentgenogram of June 12 (Figure 24) showed slight thickening of the pleura over the lateral surface of the right lung with obliteration of the costophrenic sinus.

Comment

The results obtained from the use of tryptar in hemothorax are encouraging. Tryptar can be given by thoracentesis but it is believed that

better results will be more quickly achieved with closed catheter drainage with suction. The accumulation of large amounts of fluid in the pleural cavity from proteolysis after the injection of tryptar may cause a shift of the mediastinum and cardiorespiratory embarrassment. This complication can be easily avoided by the use of a catheter. The heavier sediment in the pleural space can often be washed out with physiologic saline through the catheter before the next treatment with tryptar. The best results from the enzyme will be obtained when treatment is started immediately after hemorrhage has stopped. If organization of the clot has started, it is increasingly difficult to obtain liquefaction because the enzyme does not affect living cells. Enzymatic treatment, nevertheless, may occasionally succeed despite delay. Treatment is given at least twice a day since a considerable portion of enzymatic activity is lost within four hours. The catheter is clamped for about four hours to permit digestion after which suction is re-established. The duration of treatment is guided by the temperature curve, the color of the aspirated fluid and repeated roentgenograms of the chest. The body temperature usually returns to normal when the blood has been removed from the pleural cavity. The persistence or recurrence of fever when only serous fluid is obtained should arouse suspicions of loculated blood or pus. Tryptar should be stopped when the aspirated fluid becomes serous unless loculations are present. Repeated roentgenograms of the chest are helpful in determining whether free fluid or loculations of fluid are present.

Wounds of the lung are sealed by fibrin in the normal process of repair and therefore the creation of bronchopleural fistula from the use of tryptar is possible. This complication has not been seen.

Benedryl was given to these patients receiving tryptar to decrease the possibility of allergic reaction to the enzyme. A histamine-like response to the enzyme was not seen.

The chosen chemotherapeutic and/or antibiotic agents should be given orally or parenterally before the results of culture of the aspirated fluid are known because all traumatic hemothoraces are potentially or actually infected. The agent may be changed when the result of the culture is learned.

The principles of treatment of pyogenic empyema are essentially those of hemothorax. A thick exudate may necessitate the use of tryptar more frequently than twice a day. The proteolytic action of the enzyme on the pleural surfaces will permit better contact and more efficient action of the selected antibacterial drug. Loculations will be broken down and the enclosed bacteria opened to the chosen drug. A bronchopleural fistula in a patient with a pyogenic empyema is not a contraindication to the use of tryptar. If necessary, however, additional surgical procedures to obliterate the bronchopleural fistula, should be done.

Tuberculosis is not a contraindication to the use of tryptar. The thick pus in the empyema cavity is converted into thin material which lends itself to ready aspiration. Care must be taken when tryptar is used in tuberculous empyema in the presence of a bronchopleural fistula since the

thin pus may be aspirated into other portions of the lungs. A thick pleura, which becomes well organized and is relatively avascular, does not lend itself to proteolysis. Tryptar may be tried in such instances since, although a complete debridement may not be affected, the pleural cavity will be prepared for manual decortication.

SUMMARY

Tryptar provides the surgeon with another excellent therapeutic agent for the treatment of intrathoracic diseases. Fibrin is digested without harm to living tissues. Blood and pus are liquified and can be more easily removed. The excellent results obtained from the use of tryptar in this small series of patients with intrathoracic diseases suggests that further trial be given to the use of the enzyme in similar conditions.

RESUMEN

El triptar proporciona al cirujano un excelente medio terapéutico para el tratamiento de las afecciones intratorácicas. La fibrina es digerida sin daño para los tejidos vivos. La sangre y el pus son licuados y pueden mas facilmente extraerse. Los excelentes resultados obtenidos del uso del triptar en esta pequeña serie de enfermos con enfermedades intratorácicas sugiere que se use mas esta enzima en condiciones similares.

RESUME

Le "tryptar" donne au chirurgien une nouvelle possibilité thérapeutique excellente pour le traitement des affections intra-thoraciques. La fibrine est digérée sans créer le moindre dommage aux tissus vivants. Le sang et le pus sont liquifiés et peuvent être retirés beaucoup plus facilement. Les excellents résultats qui ont été obtenus par l'usage du "tryptar" sur un petit nombre de malades atteints d'affections intra-thoraciques que les auteurs ont suivis, font penser que des essais doivent être poursuivis dans des conditions comparables.

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A Study of the Effects of Physiotherapy in Chronic Hypertrophic Emphysema Using Lung Function Tests*

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Treatment of cases of chronic hypertrophic pulmonary emphysema has been generally regarded as a rather hopeless and unrewarding task. Apart from the use of antibiotics, oxygen and postural drainage where necessary the mainstay of rehabilitation has been the application of breathing exercises. These by focussing attention on expiration with special instruction in the use of abdominal muscles allegedly improve ventilation and diminish the state of hyperinflation of the lungs.[1,2] While it has been our experience that most patients claim to be benefitted by this form of treatment, clinical objective improvement is only rarely apparent to the unbiased observer. It seemed possible that the new hope engendered in the subject of a chronic rather hopeless incapacitating disease by the daily attention and implied optimism of the physiotherapist, might account in some measure for the patient's claims of improvement. Though it is part of the physician's function to engender this optimistic frame of mind it is also extremely important to know whether the treatment is in fact producing any real physical benefit. It was felt that this might be definitely established by the application of a group of physiological tests of lung function to a series of emphysematous subjects to see whether improvement in function could be recorded.

It was also felt that the usual form of breathing exercise might with advantage be augmented by the electrical stimulation of the abdominal and thoracic muscles during the expiratory phase. If, by electrical stimulation, the normal expiratory force could be increased it was hoped that the state of hyperinflation, characteristic of emphysema, might be diminished and improved ventilation might result. Accordingly two groups of emphysematous subjects were selected and studied before and after treatment by means of lung function tests. Treatment in the first group consisted of simple breathing exercises and in the second group of breathing exercises augmented by electrical stimulation during expiration. The object of this paper is to describe the results of these two experiments.

Material and Methods:

Fifteen subjects with varying degrees of disability resulting from chronic emphysema were selected on clinical grounds. Radiological confirmation of the diagnosis was obtained in all cases.

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TABLE I

			CLINICAL DATA						INVESTIGATIONS			
No.	Sex	Age	Asthma	Bronchitis	Previous Heart Failure	Dyspnœa	Cyanosis	Blood Pressure	Hb. (gms. pct.)	P.C.V. (c.mm. pct.)	Electro-cardiogram	Alkali Reserve Vols. Pct.
1	M	39	0	+	+	+	+	170/100	17.6	52	R.V.+	66
2	M	56	0	+	0	++	+	140/110	17.8	-	Normal	-
3	M	56	+	+	0	+	+	120/86	16.9	58	R.V.+	61
4	M	52	0	+	0	++	0	-	17.2	-	-	60
5	M	67	0	0	+	+++	+	135/80	20.5	59	R.B.B.B.	67
6	M	60	+	+	0	++	+	134/80	20.2	56.8	R.V.+	62
7	M	38	0	+	+	+++	+	118/90	20.2	-	R.V.+	-
8	M	52	+	+	0	+	+	140/90	16.4	47	R.V.+	60
9	M	75	0	+	0	+	0	135/83	14.4	42	-	49
10	F	40	+	+	0	++	+	120/80	17.5	-	Normal	60
11	M	65	+	+	+	+	+	130/90	15.8	49	Normal	56
12	M	52	0	+	+	+++	+	110/70	17.8	55.5	R.V.+	-
13	M	42	0	+	+	+	+	118/80	16.2	56	-	59
14	F	55	+	+	0	+	+	160/100	16.2	51	Normal	58
15	M	62	+	+	0	++	+	135/80	18.8	58	R.V.+	63

TABLE II

THE EFFECT OF BREATHING EXERCISES ON LUNG FUNCTION

Patient	Duration of Treatment (Days)	*Measurements Expressed as Percentage of Predicted Value* — Vital Capacity — Before	Vital Capacity — After	Vital Capacity — Pct. Change	Maximum Breathing Capacity — Before	Maximum Breathing Capacity — After	Maximum Breathing Capacity — Pct. Change	Total Capacity — Before	Total Capacity — After	Total Capacity — Pct. Change
1	13	54	71	+32	43	70	+63	115	134	+17
2	20	63	52	−18	76	47	−38	110	101	− 8
3	18	74	77	+ 4	77	75	− 3	122	121	− 1
4	20	81	75	− 7	56	72	+29	153	151	− 1
5	20	64	45	−30	44	56	+27	141	144	+ 2
6	21	80	82	+ 3	54	48	−11	124	133	+ 7
7	46	65	63	− 3	141	109	−23	121	110	− 9
8	30	64	76	+19	60	51	−15	127	127	0
9	23	103	97	− 6	114	90	−21	150	139	−17
10	24	89	67	−42	85	74	−13	144	131	− 9
Average	23.5	73.7	70.5	− 4.8	75	69	− 1	130.7	129.1	− 1
Normal Mean	±2SD	73			79			140		

TABLE II (Continued)

THE EFFECT OF BREATHING EXERCISES ON LUNG FUNCTION

	Percentage of Lung Volume									
	Functional Residual Capacity			Residual Volume			Mixing Index			
Patient	Before	After	Pct. Change	Before	After	Pct. Change	Before	After	Pct. Change	Subjective Improvement
1	78	73	− 6	61	56	− 8	10	10	0	Marked
2	74	79	+ 7	62	64	+ 3	17	14	− 2	Moderate
3	74	72	− 3	56	50	−11	21	20	− 5	Nil
4	77	78	+ 1	64	63	− 2	21	18	−14	Marked
5	86	87	+ 1	69	72	+ 4	21	28	+33	Marked
6	73	76	+ 4	55	56	+ 1	18	12	−33	Moderate
7	77	72	− 6	58	57	− 2	13	11	−15	Moderate
8	78	77	− 1	61	52	−15	27	35	+26	Moderate
9	70	73	+ 4	53	52	− 2	28	23	−18	Nil
10	77	71	− 8	60	61	+ 1	16	10	−25	Moderate
Average	76.4	75.8	−0.7	59.9	58.3	−3.5	19.2	18.1	−3.5	
Normal Mean	67			38			22.3			

TABLE III

THE EFFECT OF FARADIC MUSCLE STIMULATION OF LUNG FUNCTION

Patient	Duration of Treatment (Days)	*Measurements Expressed as Percentage of Predicted Value* — Vital Capacity — Before	Vital Capacity — After	Vital Capacity — Pct. Change	Maximum Breathing Capacity — Before	Maximum Breathing Capacity — After	Maximum Breathing Capacity — Pct. Change	Total Capacity — Before	Total Capacity — After	Total Capacity — Pct. Change
3	22	76	79	+ 4	84	88	+ 5	121	118	− 2
5	22	61	62	+ 2	38	44	+16	152	141	− 7
6	17	881	80	− 1	47	54	+15	123	124	+ 1
8	18	67	64	− 4	62	60	− 3	127	127	0
11	18	87	103	+18	92	100	+ 9	115	107	− 6
12	15	45	60	+33	50	66	+32	104	115	+11
13	24	81	89	+10	68	80	+18	111	116	+ 5
14	19	96	70	−27	140	103	−26	136	119	−13
15	20	37	37	0	65	54	−17	113	110	− 2
Average	17.6	70	71.6	+ 3.9	71.8	72	+ 6.5	122	120	−15
Normal Mean	±2SD	73			79			140		

TABLE III (Continued)

THE EFFECT OF FARADIC MUSCLE STIMULATION ON LUNG FUNCTION

	Percentage of Lung Volume									
	Functional Residual Capacity			Residual Volume			Mixing Index			
Patient	Before	After	Pct. Change	Before	After	Pct. Change	Before	After	Pct. Change	Subjective Improvement
3	74	79	+ 7	50	58	+14	30	18	−40	Moderate
5	82	86	+ 5	69	69	0	25	21	−16	Marked
6	75	73	− 3	54	55	+ 2	13	18	+40	Slight
8	78	78	0	61	61	0	34	27	−20	Marked
11	65	69	+ 6	40	38	− 5	16	17	+ 6	Moderate
12	79	72	− 9	67	60	−12	22	22	0	Marked
13	74	77	+ 4	44	42	− 5	21	25	+19	Moderate
14	70	81	+15	50	56	+12	40	19	−52	Marked
15	81	76	− 6	77	71	− 8	15	27	+80	Marked
Average	75.3	77	+2.1	57	56	−0.02	24	21.5	+16	
Normal Mean	67			38			22.3			

Clinical, electrocardiographic and haematological data are shown in Table I. Additional confirmation was obtained in all by the use of a group of lung function studies (Tables II and III).

The battery of tests used was made up as follows:

1) Spirometry was carried out before and after the administration of an antispasmodic drug (Iso-propyl noradrenaline: 5 mgm.). From this was calculated the vital capacity, maximum breathing capacity, inspiratory capacity and expiratory reserve volume, the first two being expressed as a percentage of the predicted value for the subject concerned.[5]

2) Functional residual capacity was measured by a closed-circuit constant volume apparatus of the type originally used by McMichael[3] with adaptations.[4] Residual volume was calculated by subtracting the expiratory reserve volume from the value for functional residual capacity obtained above.

3) Total lung capacity was calculated and compared with the predicted value.[5]

4) Mixing efficiency was estimated using the index advised by Bates and Christie[6] with the difference that whereas Bates and Christie adjusted all their results so that the top normal was 100 per cent, in this series the figure was calculated without this adjustment.

5) Oximetric studies (using a Waters-Conley absolute reading oximeter) to show resting arterial oxygen saturation, and the changes in saturation following on effort (±20 x 9 inch steps in one minute), maximum hyperventilation (1 minute) and inhalation of 100 per cent oxygen until the maximum rise in saturation had taken place.

In addition, a full blood count and an estimation of the alkali reserve were carried out in most patients.

It will be seen that most of the tests of function used (1-4 above) were measurements of ventilatory capacity[5] while the oximetric studies might be considered to test both ventilatory and alveolo-respiratory capacity together. It was considered that in so far as both forms of physiotherapy employed were primarily designed to improve ventilatory function, improvement could be adequately studied by the battery described above without the need of further information concerning alveolo-respiratory exchange.[7]

Cases were only selected for study after the maximum improvement possible had been obtained by the use of other methods of treatment such as antibiotics, antispasmodics and oxygen.[8] Their respiratory function was then studied for an average period of 15.5 days before physiotherapy was commenced. This allowed time for subjects to become accustomed to the tests and for the improvement associated with practice to be eliminated. After this period of pre-treatment study one of the two forms of physiotherapy to be assessed was commenced. Breathing exercises were carried out on three days per week with instructions to practice twice daily in between visits. Especial emphasis was laid on the expiratory phase, on improvement of diaphragmatic movement and on general relaxation. In the second form of treatment (referred to hereafter as "Faradic muscle

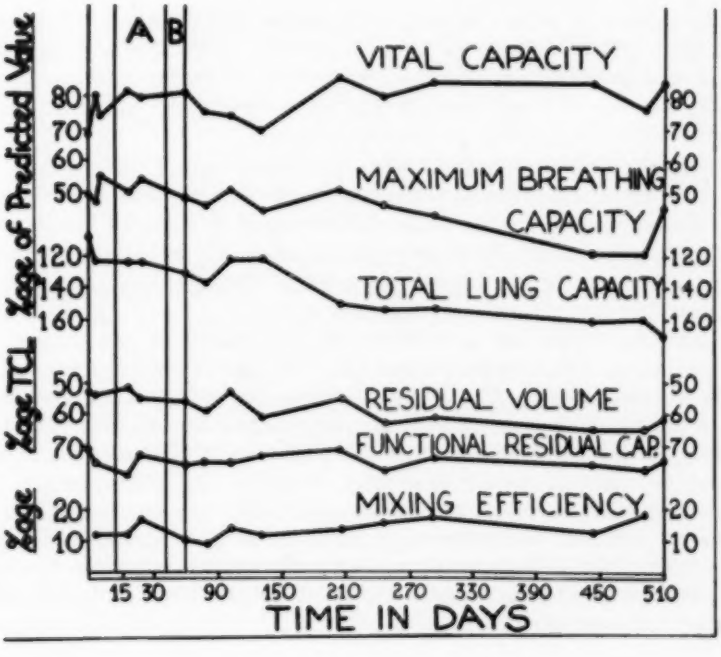
stimulation") normal breathing exercises were performed with expiration assisted by the use of faradic current applied to the chest and abdominal muscles in such a way as to produce firm contraction. The current was initiated by the patient with a press switch at the beginning of expiration.* The onset of stimulation after the switch was pressed was gradual, rising to maximum within two seconds and was discontinued at the end of expiration by the patients releasing the switch. This treatment was carried out once or twice daily for a minimum period of an hour per day.

In all, the battery of tests described above was carried out 115 times on 15 subjects, each being studied for an average of 79.8 days (range 23-205 days) with an average of 6.1 complete studies per subject (range 3-10). One or other form of treatment was carried out for an average period of 28.5 days (range 13-62 days), function studies being carried out at approximately weekly intervals. Four subjects received both forms of treatment. This was only considered permissible when the first form of treatment had produced negligible changes in function tests.

Results:

The fluctuations in values obtained over a long period of observation are well illustrated in Figure 1, where the results of the successive studies on Case 1 are graphed with the scales arranged in such a way that a rise of the graph indicates deterioration and a fall improvement. It would

*"The Electric Lung". Ludwig Schulmeister, Vienna.



appear that no significant effect has been produced by therapy, and that the case has followed a course of slow steady deterioration quite uninfluenced by the period of treatment.

For the purposes of comparison the values obtained in tests performed immediately before the commencement of the therapy were compared with the values obtained after a period of treatment lasting on an average 23.5 days (range 13-46 days), the duration of treatment being determined by such factors as the patient's enthusiasm and ability to spare the time. The change observed in each value is expressed as a percentage of the "before treatment" value, and in Tables II and III these results may be compared with the patient's subjective assessment of his own improvement.

Firstly it will be seen that all but two subjects (Nos. 3 and 9) claimed that while receiving breathing exercises they felt better and that their effort tolerance improved. In contrast, the majority of cases showed no significant change in measured values and the average percentage change for the whole group with each form of therapy can not be considered significant.

In the group receiving breathing exercises alone, only case 1 appears to have shown improvement in several values. Even in this case, however, the mixing index remained unchanged and the total lung capacity increased after treatment while the oximetric results appear to reflect deterioration (Table IV). In cases 2 and 10 there was deterioration in several values while it is impossible to detect a significant trend in any of the others.

In the group in whom breathing exercises were augmented by faradic stimulation (Table III) there was apparently significant improvement in case 12 and possibly significant improvement in some values in cases 11 and 13. In case 14 there was significant deterioration while in the rest no significant trend could be detected.

In two cases function studies were performed before and after a half-hour treatment by breathing exercises and faradic muscle stimulation. In neither was there any significant effect on vital capacity nor did treatment appear to reduce the state of inflation of the lungs in any way.

Thus far only values derived from lung capacity measurements and spirometry, and the mixing index have been considered. In none of the nine cases in whom the alkali reserve was measured before and after treatment was a fall of greater than three volumes observed. The oximetric results are recorded in Table IV. It will be seen that a significant rise (over 4 per cent[5]) in resting arterial oxygen after treatment was found in four subjects and a significant fall in five others of the 14 subjects in whom values were obtained before and after treatment. In only subjects 6 and 13 does the fall in arterial saturation after effort suggest significant improvement, while in others, notably cases 1, 2 and 12 actual deterioration is suggested. The changes produced by hyperventilation apart from case 12 in whom deterioration is suggested were surprisingly constant both before and after treatment.

TABLE IV

ARTERIAL OXYGEN SATURATION BEFORE AND AFTER TREATMENT

1) Treatment by Breathing Exercises

Case	— Resting Level — Before	After	—— Fall on Effort —— Before	After	— Hyperventilation — Before	After
1	77	79	− 4	−11	+ 5	+ 3
2	93	85	− 6	−17	+ 4	+ 8
3	93	94	− 1	− 5	+ 4	+ 5
4	93		− 7		+ 1	
5	91	82	− 3	− 8	+ 4	+ 7
6	76	83	−13	− 6	+10	+ 3
7	55*					
8	95		− 2			
9	84	87	− 3	− 2	0	0
10	93		−22		+ 7	

2) Treatment by Faradic Muscle Stimulation

Case	— Resting Level — Before	After	—— Fall on Effort —— Before	After	— Hyperventilation — Before	After
3	94	87	− 4	− 9	+ 5	+ 6
5	87	92	− 6	− 3	0	+ 2
6	81	76	−10	−13	+ 7	+10
8	87	95	− 4	− 2	+ 2	+ 5
11	95		0		+ 4	
12	82	73	− 3	−12	+ 8	− 1
13	88	93	− 6	0	+ 7	+ 5
14	85	86	− 3	− 4	+ 9	+ 9
15	87	87	− 6	− 4	+ 6	+ 5

* Direct measurement on van Slyke apparatus.

Discussion

It is soon apparent to anyone who repeats respiratory function tests at regular intervals in emphysematous subjects that in many, a definite week to week fluctuation is apparent in the values obtained. This parallels aproximately the patient's subjective state. Factors which are known to produce these fluctuations are the degree of bronchospasm, the degree of bronchial infection and the degree of heart failure. Every effort has been made to eliminate these factors as far as possible in this series. Cases with active asthma and those with symptoms of heart failure were excluded before the trial began. One subject who developed a flare up of bronchitis during treatment and deteriorated as a result was excluded as

was another who developed cardiac failure. However the tables and Figure I reflect that, as might be expected, considerable fluctuation occurred in some subjects.

To demonstrate the efficacy of a form of treatment in a group of subjects in a proportion of whom spontaneous deterioration and improvement is taking place it is necessary at least to show that during the course of treatment more cases improve than deteriorate. This we have failed to do. During the 19 courses of physiotherapy there appears to have been probable improvement recorded in two cases, possibly significant improvement in some values in two, and significant deterioration in three. It thus seems probable that the improvement recorded in certain cases was the result of natural fluctuation in the subject's condition rather than the result of therapy.

Lastly it is worthy of note that improvement was claimed by all of the three subjects in whom deterioration was demonstrated by lung function studies. We are not of course able to exclude the possibility that some aspects of lung function other than those assessed by our tests have been improved by treatment. It has seemed to us more likely, however, that the patient's claims of improvement are the result of an increased optimism and a subconscious desire to gratify those who have given him such close and careful attention during his period of treatment and study.

SUMMARY

1) Respiratory function tests have been applied to 15 emphysematous subjects on several occasions until base line values have been obtained.

2) The patients have then been subjected to one of two forms of physiotherapy: either a course of breathing exercises or a course of breathing exercises augmented by electrical stimulation of chest and abdominal muscles during expiration. Function tests have been repeated and changes assessed.

3) In all, 19 studies were carried out on 15 subjects. Though all but two claimed to feel better after treatment, function studies suggested probable improvement in only two, possible improvement in two more, and deterioration in three. In the rest no definite change was observed.

4) It was concluded that no evidence of the efficacy of these procedures had been obtained and that the benefit claimed by the subject was more likely to be the result of his mental attitude than of true physical improvement.

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RESUMEN

1) Se han aplicado las pruebas funcionales a 15 enfisematosos en varias ocasiones hasta que la linea básica de valores se obtuvo.

2) Los enfermos han sido sujetados a una o dos formas de tratamiento fisioterápico, ya sea una serie de ejercicios respiratorios o una serie de los mismos, más la estimulación eléctrica de los músculos del tórax y del abdomen durante la expiración. Se repitieron las pruebas y se estimaron los cambios.

3) En total se hicieron 19 estudios en 15 sujetos. Aunque todos declararon que se sentían mejor después del tratamiento, los estudios funcionales sugirieron probable mejoría sólo en dos, posible mejoría en otros dos y empeoramiento en tres. En el resto no hubo cambio definido.

4) Se concluyó que no había evidencia de la eficacia de esos procedimientos y que el beneficio declarado por los enfermos, era más probablemente el resultado de su actitud mental que una verdadera mejoría física.

RESUME

1) Les auteurs ont recherché les tests respiratoires chez 15 malades emphysémateux à de nombreuses reprises, avant d'obtenir des éléments de base solides.

2) Les malades ont ensuite été soumis à un ou deux modes de physiothérapie. On à utilisé soit une série d'exercices respiratories isolés, soit une série d'exercices respiratoires auxquels à été associée une stimulation électrique du thorax et des muscles abdominaux au cours de l'expiration. Les épreuves fonctionnelles ont été alors répétées, et on à noté leurs modifications.

3) Dans l'ensemble, les 15 sujets ont fait l'objet de 19 études. A part deux d'entre eux, tous se sentirent mieux après le traitement. Néanmoins, l'étude fonctionnelle montre une amélioration probable chez deux d'entre eux seulement, une amélioration possible chez deux autres, et une aggravation chez trois d'entre eux. Pour tous les autres, aucune modification n'a pu être observée.

4) Les auteurs en concluent qu'il n'y à aucune preuve de l'efficacité de ce procédé, et que le bénéfice invoqué par les malades était plus d'ordre psychique que véritablement en rapport avec une amélioration physique.

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Cor Pulmonale

A Consideration of Clinical and Autopsy Findings*

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Chronic cor pulmonale may be defined as hypertrophy of the right ventricle initiated by pulmonary hypertension. This follows increased resistance to blood flow within the lesser circulation as a result of parenchymal pulmonary disease, primary pulmonary arteriolar disease, or marked deformity of the thoracic cage. The existence of such heart disease may be recognized clinically in the presence of signs of failure of the right ventricle, or in the absence of frank failure by a combination of history, physical findings, x-ray and electrocardiographic evidence. Post mortem examination reveals right ventricular hypertrophy in a certain percentage of patients in whom clinical diagnosis has not been established.

In 1783, Senac remarked on cardiac enlargement in asthmatics. Louis, in 1830, stated that enlargement of the heart occurred in all of the cases he had seen die of emphysema who also had edema. Budd, in 1840, stressed the reduction in capillary circulation of the lungs in emphysema leading to obstruction of circulation through the pulmonary arteries, and finally to dilatation of the right heart and edema "so frequently met with in emphysematous persons". Laennec mentioned hypertrophy and dilatation of the heart and dilatation of the pulmonary artery as a sequel to emphysema. Sibson, in 1848, described autopsies on patients with emphysema dying in congestive failure with marked hypertrophy of the right ventricle.[1] In the 1920's and 1930's there was considerable controversy about the frequency and the pathogenesis of cor pulmonale. White and Brenner,[2] in 1933, remarked on the rarity of cor pulmonale. At present exact figures of the incidence of chronic cor pulmonale are lacking, but Sprague[3] remarks on its relative infrequency in the United States. He quotes the findings of White and Jones who reported in 1928 an incidence of 0.9 per cent in a series of 2,314 cases of organic heart disease in New England, and a report by White of 25 well marked cases of chronic cor pulmonale in 4,000 post mortem examinations at the Massachusetts General Hospital from 1932 to 1942.

Several articles reveal widely varying figures on the incidence of cor pulmonale, and as might be expected a quite high percentage is reported where the work is based on post mortem findings in patients with long standing severe pulmonary disease. Griggs, Coggin and Evans,[4] in a study of cor pulmonale in 1937, reviewing autopsy protocols of 18,000 consecutive autopsies, found the highest incidence of right ventricular hypertrophy in silicosis. Fifty-two per cent of 24 patients with silicosis showed right ventricular hypertrophy, with failure in 50 per cent. In 45 cases of pure

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emphysema, right ventricular hypertrophy was found in 28.9 per cent, with failure in 22 per cent. The hearts of patients with pulmonary tuberculosis showed right ventricular hypertrophy in 3.7 per cent, with definite failure in 1.8 per cent of the 1,470 cases. In 41 cases of tuberculosis with associated pulmonary lesions, particularly pneumonoconiosis, 36.6 per cent had right ventricular hypertrophy. Nemet and Rosenblatt,[5] in 1937, found exclusive hypertrophy of the right ventricle in 34 per cent of 71 cases of pulmonary tuberculosis. Kountz, Alexander and Prinzmetal,[6] in 1936, who separated and weighed the right and left ventricles of 17 patients with marked emphysema, found hypertrophy of the right ventricle in 10 of 17 cases, with hypertrophy of both right and left ventricle in most of these cases. Scott and Garvin,[7] in 1941, reviewed a series of 6,548 autopsies at the Cleveland City Hospital to determine the incidence of primary right heart hypertrophy (excluding congenital defects and regardless of the presence or absence of failure, using the thickness of the right ventricle as a criterion). In this series there were 790 who died of heart disease, of which 50, or 6.3 per cent, seemed to be cor pulmonale. Spain and Handler[8] reviewed 60 cases of cor pulmonale. In their series the leading etiologic factor was tuberculosis, followed by asthma, bronchiectasis and emphysema. A fairly large number, nine of the 60, had primary pulmonary arteriolar sclerosis. The figures on incidence of cor pulmonale in tuberculosis vary from approximately 4 to 40 per cent. Higgins[16] reported that about 30 per cent of all tuberculosis patients coming to autopsy at the Green Lake Sanitarium showed evidence of right heart failure.

The author's experience indicates that chronic cor pulmonale is a frequent and often overlooked form of heart disease. A large percentage of our medical patients are sent to Arizona for climatic relief of respiratory disease. These patients have generally experienced progressive shortness of breath with onset in the late 40's or early 50's with usually no prior history of asthma, pulmonary infection, or occupational exposure to dusts. The chief abnormal physical finding is marked emphysema. After two or three years of progressive dyspnea despite medical treatment they are either sent or come of their own volition to Arizona for climatic relief. In these patients, as well as in our tuberculous patients, cor pulmonale is a prominent feature.

From November 5, 1948, to October 29, 1951, a total of 174 autopsies were performed. In 106 of these a significant degree of cardiac abnormality was found, but not all of them had been diagnosed clinically as having heart disease. Of the 106 patients with heart disease 54 or slightly over 50 per cent were considered to have cor pulmonale from the criteria mentioned below. The most common cardiac abnormalities at post mortem, aside from cor pulmonale, were those secondary to arteriosclerosis and hypertension.

The pathological diagnosis of cor pulmonale was based on the presence of right ventricular hypertrophy, the absence of significant intrinsic cardiac disease, and the presence of sufficient pulmonary disease to act as an etiological factor. Right ventricular thickness of 5 mm. or over was regarded

as evidence of right ventricular hypertrophy. In two cases a right ventricle which measured 4 mm. in thickness was regarded as hypertrophied. In these cases the left ventricle was only 10 mm. in thickness. Hypertrophy of the papillary muscles and trabeculae carnae of the right ventricle was regarded as significant in determining abnormal degrees of right ventricular hypertrophy. Patients with hypertrophied right ventricles who also had coronary disease, or systemic hypertension with left ventricular hypertrophy, were not regarded as having cor pulmonale. Thickness of the right ventricle in this series with cor pulmonale varied from 4 to 15 mm., and the thickness of the left ventricle from 10 to 20 mm. In one a 20 mm. left ventricular thickness was associated with a 10 mm. thickness of the right ventricle. The thickest right ventricle, 15 mm., was associated with a left ventricular thickness of 18 mm. The average thickness of the right ventricle was 7.3 mm., and the average thickness of the left ventricle was 14.4 mm. The heart weight varied from 260 to 510 grams. Most of the hearts were over 400 grams in weight. In patients with arteriosclerotic and hypertensive heart disease, despite marked thickness of the left ventricle, the right ventricle was not proportionately increased in thickness. Thus, for example, a 23 mm. left ventricular thickness might be associated with a right ventricular thickness of 6 or 7 mm. The state of the heart at the time of death, whether in systole or diastole and the amount of cardiac dilatation, makes a considerable difference in the measured thickness of the ventricle. The point of measurement also makes considerable difference.

Several studies of cor pulmonale have been carried out by investigators who weighed the left and right ventricles separately. Numerous authors have remarked on the fairly consistent presence of left ventricular hypertrophy in cor pulmonale and have given various explanations for this finding. The explanation of Parkinson and Hoyle[1] is that the left ventricular hypertrophy is due to coincidental hypertension. This does not explain the finding in any of our cases, as none of them had a significant degree of systemic hypertension. Other explanations of the presence of left ventricular hypertrophy include anoxia as the significant mechanism causing left ventricular hypertrophy, and the explanation of Scott and Garvin[7] that the arrangement of muscle fibers of the right and left ventricles are such that hypertrophy of one ventricle necessitates a concomitant hypertrophy of the other.

Table I itemizes some of the data from our post mortem statistics. Slightly over 50 per cent of our patients with pulmonary tuberculosis and with other chronic pulmonary disease (chiefly emphysema) were found to have cor pulmonale. It should be noted that over 90 per cent of our deaths were autopsied during the period covered by this report. In this series of patients where pulmonary emphysema seemed to be more marked than the amount of tuberculosis, the case is included as other pulmonary disease rather than tuberculosis. It should be noted that all of the tuberculous patients with cor pulmonale had considerable emphysema. With the exception of four tuberculous patients who died following surgery or pulmonary hemorrhage, all of the tuberculous patients with cor pulmonale

died of pulmonary insufficiency or a combination of cardio-pulmonary insufficiency. Two with emphysema and cor pulmonale died of hemorrhage from gastric ulcers, and one died following surgery for traumatic intra-abdominal injuries. All of the remainder died of pulmonary insufficiency or a combination of cardio-pulmonary insufficiency. Only 13 of the 54 who showed definite right ventricular hypertrophy at autopsy were noted as being in clinical failure before death. The presence of cardiac failure could not be definitely equated with the amount of right ventricular hypertrophy, a finding analagous to that seen in systemic hypertension.

Of the 54 found to have chronic cor pulmonale at autopsy, a clinical diagnosis of cor pulmonale was made in only 21, and of the group of 54 only 13 were in clinical cardiac failure before death.

TABLE I: POSTMORTEM INCIDENCE OF COR PULMONALE AND ETIOLOGICAL FACTORS CONCERNED
Whipple VAC, November 5, 1948, to October 29, 1951

	Number Autopsied	Pct. of Autopsies	Pct. of Group	Pct. of Total Cor Pulm.
All autopsies	174	100	100	
Number with heart disease	106	61	100	
Number with cor pulmonale	54	31	51	
Number with pulmonary tuberc.	62	36	100	
Tuberc. cases with cor pulmonale	32	18	51	
Pulmonary diseases not tuberc. (Chiefly emphysema)	41	24	100	
Non-tuberc. with cor pulmonale	22	13	54	
Clinical diagnosis of cor pulmonale	21	12		38
Cor pulmonale patients in clinical cardiac failure	13	7		25

In the patient with obvious right heart failure with edema, distended neck veins, ascites, hepatomegaly and cyanosis, the diagnosis of cor pulmonale may be made readily. The diagnosis of enlargement of the right heart prior to the onset of failure is important from the standpoint of therapy and prognosis and it is a diagnosis not too readily made. Physical examination alone usually is of limited value. In the absence of failure the heart size is likely to be normal, and enlargement of the various portions of the heart cannot bo determined by physical examination in the patient with severe chronic pulmonary disease. The presence of an accentuated pulmonary second sound and a forceful sub-xiphoid pulse should be viewed with suspicion. In many cases the heart sounds are so muffled by emphysema as to be inaudible except in the sub-xiphoid region. In the absence of cardiac failure circulation time is normal. The cardiac rhythm is usually normal whether the patient is in failure or not. In only one of the cases in this series was there an abnormal rhythm, an auricular flutter in a case with cor pulmonale and tuberculous pericarditis in failure. In this

patient a catheter had been placed in the pericardial cavity believing it to be the pleural cavity, and lavage with azo-chloramide had been carried on.

The venous pressure may be elevated in emphysema in the absence of failure, or may be normal at rest and rise on exercise. This increase in venous pressure in the absence of cardiac failure has usually been ascribed to an increase in intra-pleural pressure.

The x-ray and electrocardiogram are of great value in the diagnosis of cor pulmonale prior to the onset of failure. X-ray findings are of limited value in those patients with advanced tuberculosis or silicosis which renders evaluation of the cardiac silhouette difficult, but are of considerable value in patients with emphysema. Enlargement of the pulmonary arteries is frequent, and enlargement of the pulmonary conus is frequently the first indication of cardiac enlargement. Enlargement of the body of the right ventricle is less frequently seen. The transverse diameter of the heart usually is enlarged only in the presence of failure. Angiocardiography in emphysema is reported as showing a high percentage of right ventricular dilatation.[10] The use of a barium swallow to outline the esophagus is of value in differential diagnosis of mitral disease and its accompanying left auricular enlargement. Fluoroscopy in primary pulmonary vascular disease is characterized by a large pulsating pulmonary artery and right ventricular hypertrophy.

With the routine use of 13 leads, the electrocardiogram is of great value in the diagnosis of right ventricular hypertrophy. Our accuracy in diagnosing cor pulmonale has increased since we have been taking routine electrocardiograms of tuberculous patients and medical patients with chronic lung disease using the three standard leads, unipolar limb leads, V_3R and V_1-V_6. The characteristic findings consist of high R-waves in leads over the right precordium, and deep S-waves in leads over the left precordium; depression of the S-T intervals and T-waves inversions over the right side of the heart are also of considerable diagnostic value. A high, peaked P-wave in leads 2 and 3 and the left leg lead, and the presence of a Q-wave and high R-wave in the right arm lead, are also of value in determination of cor pulmonale. Due to the markedly vertical position of the heart with clockwise rotation, the chief findings may be low to absent R-waves in chest leads V_1-V_6, with R-waves becoming more prominent as the leads are shifted one or two interspaces below the conventional levels. Electrocardiographic changes which would be equivocal if seen in a single curve become of diagnostic value when compared with previous records. Additional exploratory leads over the right chest may be of value in cases where right ventricular hypertrophy is suspected and the orthodox leads are not diagnostic. It has been our experience that the electrocardiogram will show evidence of right ventricular hypertrophy before it can be demonstrated by x-ray inspection. In a certain proportion of patients definite right ventricular hypertrophy will be found at post mortem in whom electrocardiogram and x-ray findings are within normal limits and physical examination has not revealed definite evidence of cardiac involvement.

The intensive studies of cardio-respiratory physiology[11-15] in recent years have focused attention on the circulatory and cardiac changes seen in chronic pulmonary disease, and have placed therapy on a more rational basis. The importance of acute anoxia in causing pulmonary hypertension has been emphasized. In the patient with chronic pulmonary disease the pulmonary vascular bed is reduced by the anatomic lesions, and anoxia and polycythemia further increase the disproportion between pulmonary blood flow and capacity of the pulmonary vascular bed. In the past, and as recently as 1951,[3] the grave prognosis of cardiac failure in chronic cor pulmonale has been stressed, but in our experience failure of this type may respond well to treatment consisting of the usual measures of rest, digitalization, salt restriction, mercurial diuretics and oxygen. Phlebotomy is used if the hematocrit is over 60 per cent, and antibiotics are used at the slightest suspicion of pulmonary infection. Bronchodilators (particularly ephedrine) are of value and are continued after the attack of failure is relieved. Potassium iodide is used as an expectorant.

SUMMARY

1) Autopsy findings from November, 1948, to October, 1951, at this hospital demonstrated an incidence of right ventricular hypertrophy of 50 per cent in patients with pulmonary tuberculosis and chronic emphysema.

2) Chronic cor pulmonale is much more frequently seen at autopsy than the clinical diagnosis would indicate. Awareness of the situation in which cor pulmonale is particularly prevalent, and the use of appropriate diagnostic study, should make clinical appraisal of the patient more accurate and lead to more effective treatment and more intelligent prognosis.

RESUMEN

1) Los hallazgos de autopsia de Noviembre de 1948 a Octubre de 1951 en este hospital, demuestran la frecuencia de la hipertrofia ventricular derecha que es de 50 por ciento de los enfermos con tuberculosis pulmonar y enfisema crónico.

2) El corazón pulmonar agudo es mucho más frecuente encontrado en la autopsia de lo que el diagnóstico clinico haria suponer. Una alerta sobre las situaciones en las que el cor pulmonale es particularmente prevaleciente y el uso de medios adecuados de diagnóstico, permitirán una estimación más exacta del estado clinico del enfermo asi como conducirian a un tratamiento más efectivo y a un pronóstico más inteligente .

RESUME

1) Les auteurs rapportent les constatations faites au cours des autopsies pratiquées dans leur service d'hôpital de 1948 à octobre 1951. Elles montrent la fréquence de l'hypertrophie ventriculaire droite que se vérifia chez 50% des malades atteints de tuberculose pulmonaire et d'emphysème chronique.

2) Le coeur pulmonaire apparait bien plus fréquemment à l'autopsie que ne le laisserait prévoir le diagnostic clinique. Celui-ci devrait être plus facilement porté compte tenu de la fréquence du coeur pulmonaire et de

l'utilisation des moyens d'investigation appropriés. Ainsi pourraient être établis un traitement plus efficace et un pronostic plus rationnel.

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Comments on Systemic Sarcoidosis

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The precise incidence of sarcoidosis is not known. It has been estimated that over 1,000 cases have been reported by 1948.[1] Between 1936 and 1948, 25 cases were seen in Pennsylvania Hospital and between 1947 and 1952, 21 cases were seen in the Jefferson Hospital. Among some 628,000 residents of Philadelphia of all ages, sex and color examined roentgenologically for tuberculosis during the past 10 years by the Philadelphia Tuberculosis and Health Association slightly over 2 per 100,000 presented roentgenologic findings compatible with sarcoidosis, later proved by biopsy. Although the disease is world-wide in distribution, it is more prevalent among the rural folk living in the temperate zone. In the United States, for some reason, the disease is more common in the southeastern portion, predominantly in the rural rather than in metropolitan areas. In an epidemiologic study of 226 cases of sarcoidosis in military personnel by Michael et al.,[2] 88 per cent came from the southern United States. This was true for both Negro and white groups. Even among the Negro group those born in the South showed an incidence of 25 per 100,000 inductees, as compared to an incidence of 1 per 100,000 in those with Northern birthplace and 6 per 100,000 in those from the west. This suggests that whatever the etiologic factor may be, it appears more concentrated in the southern United States. The disease has been noted in Japan, Australia, South America and South Africa. In Europe the Scandinavian countries reported most of the cases.

People of all ages are affected. Predominantly, however, it appears to be a disease of early adult life between the third and fourth decades. In the United States there is no doubt that the condition is more prevalent in Negroes; in some studies the incidence in Negroes was 16 times as great as in whites.

This disease was first described in 1875 by Hutchinson.[3] The patient was a woman named Mortimer, aged 65. The lesions consisted of a number of patches on her cheeks and back of her upper arms. The patches were raised and sharply defined on skin otherwise healthy. They were red and not ulcerated, but showed some scales. Gradually the lesions spread over the entire face. He named the condition "Lupus Vulgaris Multiplex Non-Ulcerans et Non-Surpiginosus". Fourteen years later Besnier reported the second case.

Boeck[4] of Norway reported (1894) a 36-year-old police officer in good health except for skin disease on the brow, spreading to other parts of

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the face, limbs and trunk. He removed two skin nodules each about the size of a pea and described the histologic features of sarcoid. Curiously enough, the autopsy specimens from this same patient were examined in 1947; no evidence of sarcoid was found[5] anywhere. The patient died at the age of some 80 years of hypernephroma. Heerfordt first noted fever, uveitis, parotitis and paralysis of the facial nerve. Bruins Slot suggested that uveoparotid fever was a form of sarcoidosis. Schaumann noted the disease was primarily a systemic condition and Jungling first noted involvement of the bones of the hands. The term sarcoid proposed by Boeck is derived from two Greek roots meaning "flesh" and "form".

The organs most frequently involved are lymph nodes, lungs, liver, spleen and skin. Involvement of the heart, small bones of the hands, stomach, intestines, kidneys, bladder, pituitary and thyroid glands, eyes, voluntary muscles and central nervous system has been noted.

Regardless of the tissue or organ involved, the basic lesion is always the same. It is a sharply delineated granuloma composed of uniform polyhedrol cells with abundant acidophilic cytoplasm and large, ovoid, vesicular nuclei. As the lesion matures, a narrow rim of two or three layers of fibroblasts encircle it while epithelioid cells elongate and become concentrically arranged. Regression by fibrosis then occurs, beginning as a fibrotic process between and around the individual granulomas. The fibrous tissue rapidly becomes compact, hyalinizes and forms a dense scar in which only a suggestion of the previous tubercle remains. Numerous giant cells are found within these lesions.

Some giant cells carry inclusion bodies, the Schaumann body and the spiculated body of "asteroids". Schaumann bodies are found in 3 per cent and "asteroids" in 2 per cent. Neither of the inclusion bodies is specific of this disease. Schaumann bodies are seen in the lymph nodes of lymphopathia venereum and in giant cells in the lymph nodes draining an area of regional ileitis. Asteroids occur in tuberculosis, leprosy, histoplasmosis, schistosomiasis and lipoidal granuloma. Occasional vasculization occurs in the giant cells.

Necrosis in sarcoidosis has been described as "fibrinoid" and is strongly eosinophilic. A few intact lymphocytes may occur about the periphery of the necrotic area, but otherwise the necrosis is usually acellular. Total absence of cells and cellular debris with fibrillar zones of necrosis distinguishes this from the caseation of tuberculosis. In no case of sarcoidosis has Mycobacterium tuberculosis been found.

Enlarged lymph nodes, cough, dyspnea, weight loss, skin manifestation, low grade fever, malaise and weakness, deformity of the hands when the bones are involved, conjunctivitis, poor vision, and facial paralysis are the symptoms and signs. Quite frequently the condition is suspected following roentgenological examination of the chest prior to employment. In such cases, despite pronounced changes in the lungs, the person may not have any symptom.

The cause of sarcoidosis is still unknown. Whether the disease is an atypical form of tuberculosis is one of the most controversial issues in

medicine. That it is some form of tuberculosis is more generally accepted in Europe than in America. The strongest evidence against tuberculosis as an etiologic factor is that in addition to the usual negative reaction to the tuberculin test, in no unequivocal case of sarcoidosis was Mycobacterium tuberculosis ever found. Mycobacterium leprae, Treponema pallidum, Protozoa, viruses, fungi, helminths, beryllium, foreign bodies such as paraffin, crystalline material, silica, soil, silk,[6] wool and others and certain hyperergic states of the victim with arteriolar lesions, as well as neoplastic origin and collagen disease are sometimes considered as possible causes.

Regarding some of the methods of diagnosis, a punch biopsy of the liver by means of Vim-Silverman needle and lung biopsy may be mentioned. Liver biopsy is of particular importance when the skin and superficial lymph nodes are not involved. The chief objections to needle biopsy are that serious, and occasionally fatal, complications may follow and that the small samples of tissues obtained may fail to include lesions, although actually present in the liver. The dangers are negligible, provided the procedure is carried out skillfully and precautions are taken in the selection and postoperative care of patients. There was no fatality in 650 biopsies done by Klatskin.[7] He showed close resemblance in morphology between the hepatic lesions of sarcoidosis and those of tuberculosis, erythema nodosum and brucellosis. Granulomata in tuberculosis and brucellosis exhibited greater incidence of caseation and necrosis of the tissues, and inflammatory reaction of the tissues surrounding the granulomata, but most of the lesions could not be differentiated on histological appearance alone.

Needle biopsy of the liver has definite value in confirming the diagnosis of sarcoidosis, despite the uncertainties due to the resemblance of the tissue reactions in sarcoidosis with that seen in other diseases. In Scandinavia biopsy of the tonsillar tissues is popular.

Lung biopsy apparently is a safe procedure. Under local anesthesia a small incision is made in the anterior surface of the thorax, usually between the third and fourth ribs at the anterior axillary line. Then the patient is made to inhale oxygen under positive pressure. In so doing the increased intrapulmonary pressure forces the lung to protrude through the incision. That part of the lung is tied and incised. Tissue is fixed in formalin and stained in the usual manner and examined. In over 24 pulmonary biopsies done during the past year in Jefferson Hospital by Allbritten, there was no case of pneumothorax, empyema or other complication. Patients were able to leave the hospital in 24 hours, in perfect comfort.

The so-called Nickerson-Kveim test, which is an intradermal test using 0.15 cc. of suspension of sarcoid nodules in isotonic solution of sodium chloride, is again a controversial one. In some hands this test has been satisfactory; for example, it was found to be 80 per cent positive in the series studied by Siltzbach. On the other hand, in Jefferson Hospital the test has been unreliable and, as a matter of fact, it is not used as a routine procedure in the study of sarcoidosis. One of the disadvantages of this test is that even in a proved case of sarcoidosis a definite reaction does not

take place for weeks to months. Sones[8] carried out studies on immunological reactions in sarcoidosis on 38 patients and found that patients with sarcoidosis reacted less often than controls, not only to tuberculin but also to pertussis agglutinogen, mumps virus, and oidomycin.

Hyperglobulinemia, hypercalcemia, hemolytic anemia, neutropenia, thrombocytopenia and increased sedimentation rate and pulmonary insufficiency may occur.

Treatment of sarcoidosis is unsatisfactory. Vitamin D_2, BCG vaccination, streptomycin, nitrogen mustard, urethane, tuberculin and anti-leprol have been used, but found to be of no value. Cortisone, 100 to 150 mg. daily in divided doses for a month to three months may be helpful. Upon termination of the therapy, relapses follow in the majority of cases.

Sodium intake should be restricted to 200 mg. a day for hospitalized patients and 500 mg. for ambulatory patients. A potassium supplement may be given in the form of the chlorides, 3 gm. daily. In the cases of ocular lesions it is imperative that the drug be used. In uveitis, particularly if the anterior segments are involved, drops of cortisone may be instilled directly into the eye or underneath the conjunctiva. However, if the posterior segments are involved, then ACTH intraveneously, or cortisone orally in tablet form, is used. The effect of these treatments appears to be satisfactory.

As far as prognosis is concerned, many seem to recover spontaneously only to relapse later on. It has been estimated, however, that about 30 per cent recover permanently. This again is open to question. Some develop congestive heart failure resulting from cor pulmonale and about 25 per cent of them develop fatal pulmonary tuberculosis. In such a case there is always a doubt whether the condition was not tuberculosis from the beginning.

SUMMARY

Sarcoidosis is a disease of unknown cause. The basic morbid anatomy regardless of the organ or tissue involved is the epithelioid cell tubercle without necrosis, having refractile or calcified inclusion bodies in the giant cells.

Lesions are usually widely disseminated. The tissues most frequently involved are lymph nodes, lung, liver, spleen, skin, eyes and bones, particularly of the hands. The heart, striated muscles, stomach, intestines, kidneys, bladder, pituitary and thyroid glands, and central nerves may also be involved.

The clinical course is usually chronic with minimal or no constitutional symptoms; however, there may be acute episodes of fever and malaise with or without signs or symptoms referable to the tissues and organs involved.

The intracutaneous tuberculin test is usually negative; the plasma globulins are often increased.

The outcome may be clinical recovery with radiographic evidence of residue, or impairment of function of organs involved, or a continued

chronic course of the disease. Treatment is unsatisfactory. Prognosis is uncertain.

RESUMEN

La sarcoidosis, es una enfermedad de causa desconocida. La anatomía patológica básica sin tener en cuenta el órgano o tejido comprometidos, es el tubérculo de celdillas epitelioides sin necrosis, que contiene cuerpos de inclusión refractiles o calcificados en las celdillas gigantes. Las lesiones habitualmente están ampliamente diseminadas.

Los tejidos más frecuentemente afectados son los ganglios linfáticos, el pulmón, el hígado, el bazo, la piel, los ojos y los huesos especialmente, los de las manos. El corazón, los músculos estriados, estómago, intestinos, riñones, vejiga, la pituitaria, la tiroides y el sistema nervioso central, pueden también ser afectados.

La evolución clínica, es generalmente crónica con síntomas generales mínimos o ningunos; sin embargo, puede haber episodios agudos con fiebre, malestar con o sin síntomas referibles a los tejidos u órganos afectados.

La reacción intracutánea de tuberculina, es habitualmente negativa.

Las globulinas en el plasma, a menudo están aumentadas.

El resultado final, puede ser la recuperación clínica con evidencias de residuos radiográficamente o bien hay una evolución crónica de la enfermedad. El tratamiento no es satisfactorio. El pronóstico es incierto.

RESUME

La sarcoïdose est une maladie de cause inconnue. Le substratum anatomique de la lésion, indépendamment du viscère ou du tissu atteint est le tubercle épithélioide sans nécrose avec dans les cellules géantes, des inclusions de corps réfringents ou calcifiés. Les lésions sont habituellement largement disséminées. Les tissus le plus souvent atteints sont les ganglions, le poumon, le foie, la rate, la peau, les yeux et les os, en particulier ceux de la main. Le coeur, les muscles striés, l'estomac, les intestins, les reins, la vésicule biliaire, les ganglions hypophysaires, et thyroïdes ainsi que le système nerveux central peuvent être également atteints.

L'allure clinique est généralement chronique, ne s'accompagnant que de symptômes minimes ou peu caractéristiques. Toutefois, il peut y avoir des épisodes aigus, de la fièvre et des troubles généraux comportant ou non des symptômes dûs à l'atteinte de certains tissus ou de certains organes.

Habituellement, les réactions tuberculiniques sont négatives. Souvent, il y à augmentation fréquente des globulines plasmatiques.

L'évolution peut se faire vers une guérison clinique s'accompagnant de séquelles radiographiques ou vers un trouble fonctionnel des organes atteints ou encore vers la chronicité de l'affection. Aucun traitement ne donne satisfaction. Le pronostic est incertain.

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Unusual Lung Conditions Simulating Tuberculosis*

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This is a paper from "Bella Vista" Sanatorium of Asunción, Paraguay, for tuberculous patients. In seven years, from 1945 to 1952, 1,246 patients have been discharged of whom 100 (8 per cent) were non-tuberculous. Some of these patients were sent as tuberculous, some others were admitted with diagnostic doubts for further study, but could simulate more or less tuberculosis.

100 PATIENTS WITH CONDITIONS SIMULATING TUBERCULOSIS

1) Inflammatory Diseases		35
Acute pneumonopathy	14	
Fibrosis	4	
Transient infiltration	3	
Loeffler's syndrome	6	
Abscess of the lung	7	
Pneumoconiosis	1	
2) Tumors		16
Primary cancer of the lung	8	
Metastatic cancer	2	
Metastatic pleural tumor	2	
Cancer of the esophagus	1	
Endothoracic goiter	1	
Hamartoma of the lung	1	
Indeterminate tumor	1	
3) Broncho-Pulmonary Malformations		13
Pulmonary agenesis	1	
Alveolar agenesis	6	
Polycystic lung	2	
Emphysema with giant bullae	4	
4) Bronchial Diseases		13
Foreign body	1	
Bronchiectasis produced by foreign bodies	2	
Bronchiectasis	11	
5) Pleural Diseases		7
Benign pneumothorax	2	
Cholesterine pleurisy	2	
Traumatic empyema	2	
Traumatic pneumothorax	1	
6) Foreign Bodies in the Lung		4
7) Without Pathologic Alterations		6
Without alterations	3	
Positive sputum previous to admittance, but negative afterwards	3	

8) Miscellaneous		6
Banti's disease	1	
Purulent pericarditis	1	
Acute endocarditis	1	
Pulmonary infarct	1	
Sarcoidosis	1	
Indeterminate abdominal lymphangitis	1	

SUMMARY

One hundred cases of non-tuberculous conditions are reported. They were patients admitted to "Bella Vista" Sanatorium of Asunción, Paraguay, sent to us as tuberculous cases or for a better study. The 100 cases are divided in the following categories: 35 inflammatory diseases; 16 tumors; 13 malformations; 13 bronchial diseases; 7 pleural diseases; 4 foreign bodies; 6 without disease; 6 miscellaneous.

RESUMEN

Se relatan cien casos de afecciones no tuberculosas. Se trata de casos de enfermos ingresados al Sanatorio Bella Vista de Asunción, Paraguay, que nos han sidos enviados para mejor estudio como afectos de tuberculosis. Los cien casos se agrupan como sigue: 35 de afecciones inflamatorias; 16 tumores; 13 malformaciones; 13 afecciones bronquiales; 7 afecciones pleurales; 4 cuerpos extraños; 6 sin enfermedad; 6 diversos.

RESUME

Les auteurs rapportent 100 observations de malades non tuberculeux. Il s'agissait de malades hospitalisés au Sanatorium Bella Vista d'Asuncion (Paraguay) avec le diagnostic de tuberculose ou pour mise en observation. Les 100 cas se répartissent comme suit: 35 affections inflammatoires; 16 tumeurs; 13 malformations; 13 affections bronchiques; 7 affections pleurales; 4 corps étrangers; 6 sans aucune affection; 6 divers.

Left Heart Failure in the Newborn

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The development of acute left heart failure in the newborn is rather an unusual event. It is apparent that only a few diseases can produce sufficient strain on the left ventricle to produce this particular syndrome. In the presence of left heart failure in the newborn, one should suspect coarctation of the aorta as a cause. It has been stated both by Blackford and by Abbott that coarctation of the aorta is of little clinical significance in infancy. They predicate this belief on the fact that in the two types of coarctation, the infantile type is fatal because of other associated severe anomalies of the heart, and the adult type has sufficient circulation to carry on the normal functions of the cardiovascular system. Aortic coarctation may be classified according to the relationship of the stricture in the aorta to the ductus arteriosum. A coarctation may have the stricture proximal to the aortic mouth of the ductus, or at the level of the ductus or distal to the ductus. Since the constriction exists before the birth of the child, it is obvious that the position of the ductus is very important in determining the degree and extent of the collateral circulation that develops. Evidence suggests that collateral circulation occurs whenever the demand fo rit is present. It is possible for such collaterals to be present before birth. In failure of development of adequate collateral circulation it becomes apparent that a strain may be placed on the left heart and left heart failure may appear. The two following cases of coarctation of the aorta in the newborn associated with acute heart failure are presented:

Chart No. D-81453, Autopsy No. A-51-6. Baby Girl R.

The baby was born on the 2nd of February 1951, at 2:30 A.M. and died at 11:30 A.M. on the same day. At 8:30 A.M. on the day of birth, the child seemed to have a mild cyanosis and a strangling type of cry. Occasionally, the patient had a convulsion. The physical examination was negative. The abdomen was distended but no rectal obstruction was found. The child began to vomit bloody-green mucus and the reflexes became hyper-active. The platelet count at 5:30 A.M. was 170,000. The patient was given parathyroid, penicillin, and supportive measures. The blood sugar was 70 mgm. The child had more convulsions and then developed a paraxysmal dyspnea and finally the dyspnea became marked and was associated with cyanosis and ultimately rales were present in the chest. Bloody mucus escaped from both the nose and mouth terminally. The Wasserman test was negative. The hemoglobin was 94 per cent, the red count 4,800,000, the white count 32,600 and the differential count was normal. An x-ray film of the chest was unsatisfactory because of motion. The only finding of interest at necropsy was in the heart. There was a marked coarctation of the aorta. The aorta itself exhibited a curtain-like constricting ring extending transversely across the lumen approximately 1 cm. distal to the left subclavian artery. This

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constricted area of the aorta was opened and it was one-third of the width of the normal aorta indicating that the circumference of the aorta was not over at the most one-third of normal size. The ductus arteriosus was patent and was normal in appearance and in position. On microscopic examination nothing of note was found except for marked pulmonary edema.

Chart No. B-AO 231, Autopsy No. A-5123.

The patient was born six weeks before admission to the hospital on December 1, 1950 and death occurred on the 19th of December 1950 at 8:10 A.M. At three weeks of age, the parents noted the child had no desire to eat, had lost weight and was obviously dyspneic. The infant was large at birth and fed well while in the nursery, but on going home, the child began to fail in health. The child had difficulty in breathing. This dyspnea was evident on admission to the hospital. The dyspnea was mild at the start and then increased in severity. On physical examination, the child was very ill and rales could be heard in the left lung. The heart tones were normal and no masses could be found. The hemoglobin was 87 per cent, the red count 4,520,000, the white count 19,000, and the differential count was normal. The child was given oxygen. The x-ray examination revealed an enlargement of the heart. The urine revealed 2+ albumin, 4+ sugar with a trace of acetone. The white blood count on the day following admission was 27,400 and the hemoglobin was 103 per cent. The child developed a pneumonia which responded to treatment. On the 11th of December, rales appeared in both lung fields. On the 13th of December, the child had weakened and the dyspnea had increased and the child died on the 19th hospital day. The heart weighed 80 grams and showed marked hypertrophy of right and left ventricular walls. The enlargement on the right was more marked than that of the left. There were no abnormalities in the heart itself but the pulmonary artery was quite ectatic. The coronary circulation was normal. The root of the aorta was normal and opened into the pulmonary artery by a very wide ductus. The vessels that went to the neck were greatly dilated. There was a very marked constriction of the aorta just distal to the left subclavian artery representing a typical coarctation of the aorta. The pulmonary artery was dilated. The pancreas on close examination showed nothing remarkable but on microscopic examination, there was extensive interstitial fibrosis with dilatation of some of the ducts and these were filled with precipitated protein. The final diagnosis was coarctaton of the aorta with patent ductus arteriosus and congestive heart failure as well as cystic fibrosis of the pancreas.

Conclusions: The recognition in infancy of coarctation of the aorta as a cause of left heart failure is imperative, for immediate surgery can cure the condition. This is a feasible operation and can be readily accomplished if one recognizes the inherent nature of the heart failure and the possibility that coarctation of the aorta is the underlying cause of the heart failure.

SUMMARY

Two cases are reported in which left heart failure occurred in early infancy as a result of coarctation of the aorta. The salient clinical features are noted and the criteria for diagnosis is emphasized.

RESUMEN

Se describen dos casos en los cuales se observa insuficiencia del corazón izquierdo en la primera infancia como resultado de la coartación de la

aorta. Las caracteristicas clinicas más sobresalientes, seran detalladas y se hara mención especial de los criterios para el diagnostico.

RESUME

On rendra compte de deux cas où un arret à la gauche du coeur s'est declaré dans la première enfance comme résultat de la coarctation de l'aorte. Les principaux symptomes seront notés et les criteriums du diagnostic seront signalés.

Hamartoma Simulating Ipsilateral Metastasis in a Case of Primary Bronchogenic Carcinoma

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Although primary carcinoma of the lung is fairly common, representing about 10 per cent of all carcinoma cases seen at autopsy,[1] the co-existence of a benign pulmonary hamartoma must be rare. Fortunately, in the case to be presented, the two lesions were in the same lung so that pneumonectomy removed both tumors. Had the benign lesion been in the contra-lateral lung, it would have been considered to be a metastasis from the bronchogenic carcinoma and the patient would have been denied the benefit of surgery.

Case Report

D.K. Case 144698. A 71 year old white male was admitted to the Thoracic Surgical Service of the Hospital for Joint Disease on March 27, 1951 with a history of having had productive cough and fever three weeks prior to admission. At that time, physical examination revealed signs of pneumonia of the lower lobe of the left lung which was treated with penicillin. The symptoms disappeared but roentgen examination revealed a residual infiltration lesion of the left upper lobe which was suggestive of pulmonary neoplasm and hospital admission was recommended.

Past History was negative except for benign prostatic hypertrophy which was treated at another hospital two years previously by supra-pubic prostatectomy. Upon admission, he presented no weight loss, hemoptysis or expectoration.

Physical Examination revealed dullness to percussion of the left chest down to the level of the third thoracic spine with diminished breath sounds and vocal and tactile fremitus. No adenopathy was present. The remainder of the examination was negative.

Laboratory examinations of urine, blood, non-protein nitrogen, total protein, inorganic phosphatase, alkaline phosphatase, acid phosphatase and chlorides and hemogram were all within normal limits.

Roentgenograms of the chest taken April 4 (Figure 1) and laminograms on April 7, 1951 (Figure 2) showed a large globular area of infiltration extending from the hilum of the left lung into the apex at the level of the second intercostal space. In addition, a large fibrotic nodule or area of infiltration was noted in the plane of the fourth intercostal space. This was interpreted as probable bronchogenic carcinoma of the left upper lobe with adjacent pneumonitis and ipsilateral metastasis. Roentgenographic examination of the long bones was negative for metastases.

Bronchoscopy was performed on April 16, 1951 and revealed the trachea deflected to the right with visualization of the left upper lobe orifice not possible due to the anatomical arrangement. No infiltration, obstruction or neoplasm was noted within the range of bronchoscopic vision and no biopsy was taken. Papanicalou smears from the left main bronchus showed no abnormal or atypical cells.

Sputum Examination by the Papanicalou method, however, showed occasional clusters of deeply staining cells with hyperchromatic nuclei. These were considered as atypical cells but without malignant features.

Operation was performed on April 28, 1951 under endotracheal ether, cyclopropane anaesthesia in the "face-down" position. The sixth rib as well as a short posterior segment of the fifth were removed. The pleural space could not be

entered due to synechias between visceral and parietal pleurae so that an extrapleural approach was used and a pleuro-pneumonectomy performed. After the apex was brought down by blunt and sharp dissection, the mediastinum was found to be flaccid and uninvolved except for some large, soft, edematous lymph nodes which were removed with the lung. Individual cotton ligatures were used on vessels, and five silk plication sutures on the bronchus in the manner of Overholt.[2] The pleural cavity was thoroughly irrigated with saline and one tube dependent thoracostomy performed. Silk was used in layers for closure.

Post-operative Course: The drainage tube was removed after 24 hours. On the second post-operative day, he became slightly dyspneic and his skin was found to be cold and moist despite normal temperature and blood pressure. The pulse was grossly irregular and an electrocardiogram revealed many supraventricular premature contractions. He was digitalized with digoxin but maintained a tachypnea and fine moist rales at the right base for two weeks post-operatively (Figure 3). On May 30, 1951 he was discharged to a convalescent home where he remained for several weeks prior to returning home. He was seen at the Thoracic Surgical Clinic on October 18, 1951 where roentgenogram revealed obliteration of the left hemi-thorax by diffuse opacity without fluid level and only slight ipsilateral shift of the mediastinum; the right lung appeared normal. He had no complaints. There was no dyspnea on ordinary activity and the heart showed regular sinus rhythm. No lymph nodes were palpable.

Specimen: The lung was cut immediately after pneumonectomy, and unfortunately in doing so it was rendered unsuitable for photography. An irregular area of consolidation was present involving about two-thirds of the left upper lobe and extending into the apex. The upper lobe bronchus was patent for about 0.5 cm. and was occluded at this point by a friable whitish mass which infiltrated the bronchial wall. Upon pressure over the substance of the induration, a moderate amount of green, purulent material could be expressed. The indurated area extended almost to the visceral pleura at the periphery and contained numerous dilated bronchi and small saccular and cylindrical cavities which represented bronchiectasis and early abscess formation. The surrounding pulmonary parenchyma was atelectatic, firm and showed marked evidence of inflammatory exudate, which extended to the interlobar fissure and the pleura. In the area of the lingula and 0.5-0.7 cm. below the anterior visceral pleura was a round 1.3 by 1 by 1.2 cm. circumscribed nodule of whitish semi-gelatinous tissue which could be enucleated from the lung parenchyma with ease. The surrounding pulmonary parenchyma was not adherent and was smooth after the nodule was enucleated. The nodule itself presented a rather friable center surrounded by whorls of thickened whitish tissue. The central area was more gelatinous or mucoid than the peripheral portion.

Microscopic examination revealed a rather well differentiated epidermal carcinoma of the left upper lobe bronchus with atelectasis and acute and chronic inflammation of the peripheral lung parenchyma (Figure 4). The nodule was found to be composed of irregular strands and islands of cartilage interspersed with fat cells, fibroblasts, smooth muscle fibers and bronchial mucosa (Figure 5). This was considered to be a benign hamartoma.

Discussion

Warren and Gates[3] found 6.8 per cent of 2,829 autopsies on patients with carcinoma disclosed multiple primary lesions. Cahan, Butler and Watson[4] reported 20 cases of multiple primary carcinomata, one being a triple primary—breast, sigmoid and lung. Hochberg, Grayzed, Berson and Rosenberg[1] reported a fascinating case in which a fibrosarcoma and carcinoma were present in one lung with a hamartoma in the other. In addition, there

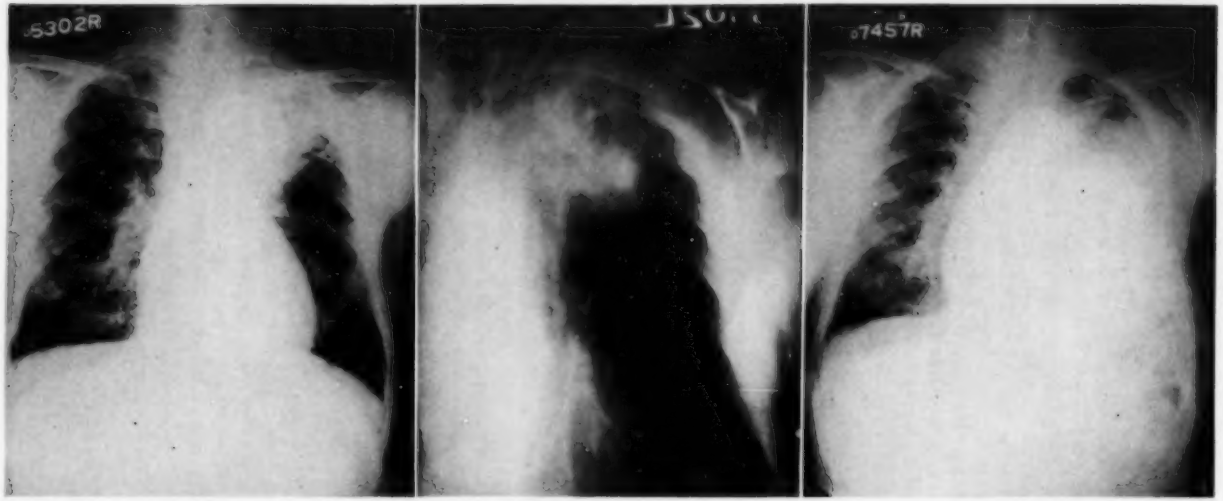

FIGURE 1 FIGURE 2 FIGURE 3

Figure 1: Pre-operative roentgenogram showing infiltrating lesion left upper lobe and solitary nodular density (Arrows). *Figure 2:* Pre-operative laminogram.—*Figure 3:* Roentgenogram on 12th post-operative day. Subsequent films show disappearance of fluid levels and subcutaneous emphysema.

were several benign tumors in six other organs. Unfortunately, no roentgenograms were published.

Albrecht in 1904 introduced the word "hamartoma" for a benign mixed tumor occurring in various organs including the lung. He considered these lesions not to be true tumors, but rather tumor-like structures composed of normal tissue of the organ arranged in an abnormal way or developed abnormally and showing varying degrees of differentiation of the individual tissues. The term "chondroma" still appears in articles[5] describing lesions such as these and should probably be discarded in favor of the more descriptive and accurate term "hamartoma." Bragg and Levine[6] found that abuot 100 pulmonary hamartomata have been reported mostly under the name of "chondroma". Of these, 75 per cent were discovered incidental to autopsy while the remainder were surgical findings. Less than 10 per cent, however, were correctly diagnosed pre-operatively.

It might be assumed that the tumor is a rare one from the small number of cases reported. That this is not so is confirmed by McDonald, Harrington and Clagett[7] who reported 23 cases from the Mayo clinic of which 20 were found incidentally at 7,982 necropsies and three were diagnosed correctly pre-operatively. This represents an incidence of 1 in 400 autopsies. Bragg and Levine[6] feel that the incidence of this tumor is greater than that of bronchial adenomata and is second only to bronchogenic carcinoma. Bronchial adenomata are more rapid in their growth, occur in larger bronchi and cause symptoms of obstruction and bleeding while hamartomata, on the other hand, are slow growing, usually sub-pleural and are not likely to produce symptoms leading to their discovery.

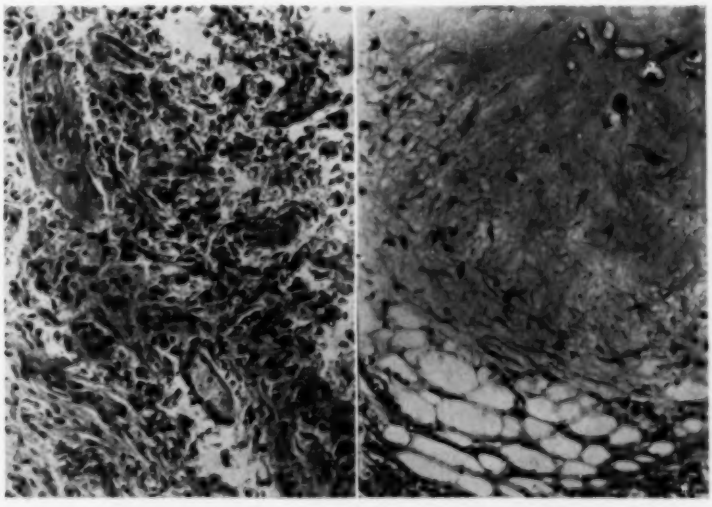

FIGURE 4 FIGURE 5

Figure 4: Photomicrograph showing well differentiated epidermoid carcinoma of lung.—*Figure 5:* Photomicrograph showing benign hamartoma.

Hamartomata are found three or four times as frequently in males as in females and have occurred in all ages from nine to 87 years. The distribution is roughly proportional to the relative size of the lobes, so that the lower lobe of the right lung is the most common location. They are most often solitary, the nodules ranging in size from a few mm. to 9 cm., the majority ranging from 0.5 to 3.0 cm. Simon and Ballon[8] report an 11 by 8 cm. hamartoma with obstructive symptoms causing pneumonia, bronchiectasis, brain abscess and meningitis which was erroneously considered to be a bronchogenic carcinoma. Though these tumors are practically always solitary, Ewing[9] quotes Virchow as describing multiple chondromata of the lung located at the root, in the parenchyma and on the pleura.

The gross appearance is characteristic. They are lobulated, round or spherical, sharply delineated from surrounding lung tissue and usually bound by a discrete capsule which strips easily. The cut surface is avascular, whitish, never anthracotic, with the consistency and appearance of layers of cartilage separated from other tissues. Areas of calcification or islands of bone formation may offer resistance to cutting.

The microscopic picture is also characteristic. The most prevalent tissue is cartilage arranged in irregular islands, sheets or strands or less commonly as a solid mass of cartilage. The irregular islands of cartilage are usually separated by areas of connective tissue, some of which are in various stages of mucoid degeneration and have an appearance not unlike mesenchymal tissue. Interspersed throughout, there may be epithelial or glandular tissue elements resembling that of small bronchi lined by simple cuboidal or columnar cells which may be ciliated. These glands occasionally produce mucous pockets. Fibrous tissue, smooth muscle and bone are occasionally present and it is not unusual to find scattered groups of mature fat cells, especially at the periphery (Figure 4).

Diagnosis by roentgenogram is not always possible but should be made more often than it has been in the past. The appearance of a solitary sharply demarcated round or spherical tissue with lobulated margin surrounded by normal lung tissue usually located peripherally or sub-pleurally and occasionally showing patchy areas of calcification on tomogram with areas of lesser density or fuzziness at the periphery should be suggestive of a hamartoma.

Since malignant change in a hamartoma is rare, the importance lies in differentiating this from other dangerous lesions. Of these, bronchogenic carcinoma is most important to rule out. The latter are faster growing and if calcification is present, bronchogenic carcinoma is unlikely. A solitary pulmonary metastasis may be impossible to differentiate from hamartoma without calcification, as in the case presented. Since solitary metastatic lesions are now resected in selected cases,[10,11] thoracotomy and frozen section may decide between simple enucleation and radical lobectomy or pneumonectomy. Bronchial adenoma may occasionally resemble hamartoma, but symptoms of bleeding, obstruction, hilar location and bronchoscopy should ensure diagnosis. Pulmonary "tuberculomata" may be indistinguishable from hamartomata, especially since areas of calcification may

be seen in both. When a history of tuberculosis is not obtainable, the presence of a peri-tuberculomatous inflammatory reaction may present a fuzziness or haziness so that they may occasionally be indistinguishable from hamartomata. As more tuberculomata are resected many additional hamartomata will be discovered.

ADDENDUM

The patient expired on August 24, 1952. Autopsy revealed metastases to tracheal lymph nodes and liver with invasion of right diaphragm. Bronchial stump showed no carcinoma. An incidental finding was a thyroid adenoma.

SUMMARY

A case is reported of primary bronchogenic carcinoma with co-existing hamartoma of the same lung in a 71 year old male. Pre-operatively, the benign lesion was thought to be an ipsilateral metastasis and pneumonectomy was successfully performed. Fortunately, the two tumors were in the same lung. Otherwise, the lesions would have been considered inoperable. The possibility of multiplicity of tumors, benign or malignant, has been stressed.

RESUMEN

Se refiere un caso de carcinoma bronquiogénico primario con hamartoma coexistente en el mismo lado pulmonar en un hombre de 71 años. Antes de la operación la lesión benigna se creyó que era una metástasis ipsilateral y la neumonectomía fué realizada con exito. Afortunadamente los dos tumores estaban en el mismo pulmón pues de otra manera se hubiera considerado un caso inoperable. Se reclaca la posibilidad de la existencia de tumores múltiples benignos o malignos.

RESUME

Les auteurs rapportent l'observation d'un homme de 71 ans, atteint d'un cancer primitif des bronches associé à un hamartome du même poumon. Avant l'intervention, la tumeur bénigne fut considérée comme une métastase et l'on pratiqua avec succès une pneumonectomie. Il est heureux que les deux tumeurs se trouvaient dans le même oumon. Dans l'autre cas, les lésions auraient été considérées comme inopérables. Les auteurs insistent sur la coexistence possible de tumeurs multiples, les unes bénignes, les autres malignes.

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Massive Pulmonary Hemorrhage Due to Sarcoidosis

Report of Two Cases*

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Sarcoidosis continues to be a perplexing disease, the etiology of and the treatment for which remain obscure. No longer is the name "benign lymphogranulomatosis" applicable, for it is now known that sarcoidosis is capable of producing irreversible destructive changes and may per se be responsible for death. Since this disease may affect any organ of the body, it is understandable that symptoms and signs referable to the organ involved can and do simulate those of other more common disease-states involving these organs. Although pulmonary involvement due to sarcoid is common, certain forms are distinctly unusual and the diagnosis under such circumstances can be elusive. The clinical background and the character of the pulmonary lesions in the two cases presented were so confusing that reporting them seemed to be warranted.

Case 1: L.M. (or L.A.), a colored woman, age 33, was first seen at the Jefferson Hospital during October 1948. At that time she was found to have extensive pulmonary disease with left pneumothorax (Figure 1). Although she recalled having had no pulmonary complications following illnesses in childhood, she was certain that clubbing of the fingers had been prominent since approximately the age of 15. Approximately four years previously she had migratory arthritis and recurrent tender "spots" on her skin which subsequently left depigmented areas. This condition was repeatedly referred to by internists and dermatologists as vitiligo. There had been no known exposure to tuberculosis, she had not traveled in the coccidioides belt and there was no history of occupational exposure. For years she had been employed as a cook in a small restaurant.

In February 1950, when she consulted a chest specialist because of increasing cough and shortness of breath, numerous sputum examinations for tubercle bacilli and tuberculin skin tests were negative. She was told that the x-ray examination of the chest demonstrated extensive cystic changes and that she had cystic disease of the lung. By April 1950 (Figure 2) cough and dyspnea were ingravescent. She was so short of breath that she had to sleep in the erect position and she could not speak a full sentence without having to stop to catch her breath. Coughing spells were worse in the morning upon first getting up and upon lying down in the evening. She estimated that she raised approximately a cupful of purulent sputum daily and had observed blood-streaking at t imes. During the past year she lost approximately 20 pounds. There had been non-seasonal wheezing, worse at night, and intermittent attacks of watery nasal discharge. In spite of all of these difficulties she had continued to work regularly.

In May 1950, the temperature was normal, the pulse rate was 124, respirations were 34, the blood pressure was 90/70 and her weight was 100½ pounds. She was a tall, slender, well developed but poorly nourished Negress. Pallor of the mucous membranes, clubbing of fingers and toes and patchy distribution of vitiliginous lesions, localized for the most part over the arms and the upper half of the torso, were immediately obvious. No peripheral adenopathy was observed. The chest was long and thin with gross deficiency of subcutaneous tissue. Respiratory excursions

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FIGURE 1 FIGURE 2 FIGURE 3

Figure 1: Demonstrates extensive bilateral bullous emphysema, patchy pneumonic infiltration, bilateral pleural reaction, broadened right upper mediastinal shadow and spontaneous left apical pneumothorax.—*Figure 2:* Shows disappearance of pneumothorax, variations in emphysematous blebs and pneumonic densities. The right upper mediastinal shadow is still prominent.—*Figure 3:* Great variation in size, shape and extent of emphysematous bullae and pneumonic densities. There is now obvious cardiac enlargement. The tremendous increase in bleb formation is obvious.

were limited and there was dullness over the right side posteriorly. There was great variation in the character of breath sounds—over some areas classical emphysematous breathing was heard; elsewhere breath sounds were entirely absent. Constant moisture was heard over both lower lung fields but without wheezes. The only discernible abnormalities on examination of the heart were the rapid rate and a significant increase in the intensity of the second pulmonic sound. The liver and spleen were not palpably enlarged and there was no edema.

Basic laboratory data disclosed normochromic anemia, leucocyte count of 9,300 cells/cmm. and differential count well within normal limits save for 9 per cent eosinophils. The urine was negative. Numerous sputum studies were negative for acid-fast organisms but a direct study of the sputum was reported as being loaded with monilia. The blood Kahn test was negative.

Over a period of several weeks she was given large doses of iodides and an antihistamine with subjective and objective improvement in cough, expectoration, shortness of breath and vasomotor rhinitis. During July 1950 increased pulmonary bleeding occurred at the time of her menstrual period. Two days prior to the onset of the next menstrual period there began significant pulmonary bleeding which ceased spontaneously with the cessation of menstruation. Subsequent to that time she had large pulmonary hemorrhages on several occasions not associated with menstruation. She was lost sight of until February 1951 when she came to the Hillman Hospital Clinic because of abnormal vaginal bleeding of two months duration. Menstrual periods had ceased several months previously followed by some spotting. A clinical diagnosis of cancer of the cervix was confirmed by tissue study and she was given a course of x-ray therapy followed by radium.

On July 7, 1951, she was admitted to the Hillman Hospital because of profuse pulmonary bleeding. Sputum studies again disclosed monilia in profusion. On two occasions a rare acid-fast organism was suspected on concentrated material but three cultures of the sputum for tuberculosis and tuberculin skin tests remained negative. The admission hemogram was as follows: hemoglobin 9.7 gm. (63 per cent), red blood cells 4.36 million, leukocytes 5,700 with a differential count of mature polymorphonuclears—68, stab forms—5, lymphocytes—17, monocytes—1, eosinophils—5, basophils—4 per cent. The corrected sedimentation rate (Wintrobe) was 43 mm./hr. The urine showed one plus albumin and 5-6 wbc./hpf. Total proteins were 7.6 gm. per cent with 2.7 albumin, 4.9 globulin and a ratio of 1:1.8. The blood urea nitrogen was 19 mg. per cent. Biopsy of a vitiliginous lesion was interpreted as being consistent with sarcoidosis. X-ray films of the hands and feet showed "cystic and lace-like trabeculations in the phalanges consistent with the diagnosis of Boeck's sarcoid." She was discharged on July 25.

Again she was lost sight of for a number of months but was admitted to the St. Vincent's Hospital in Birmingham on December 7, 1951, because of large pulmonary hemorrhages which continued briskly for two days after admission (Figure 3). Apparently she withheld information with reference to her previous hospitalizations. Laboratory data disclosed a profound anemia but no tubercle bacilli. Bronchoscopy revealed rotation of the bifurcation to the left, and a bloody discharge from the right upper and lower lobes. No tumor cells were found. She was discharged on December 27, 1951, and went to another city where she died several days later. Necropsy was not obtained.

Comment: There are several points of interest in addition to the character of the pulmonary lesion and the gross pulmonary hemorrhages. There is a long-standing history of digital clubbing which obviously was present years before the onset of pulmonary symptoms. Pneumothorax has been reported in sporadic cases of sarcoidosis. It is of interest that the vitiliginous lesions still showed changes consistent with sarcoidosis. This experience indicates the wisdom of obtaining biopsies of presumably simple skin lesions

in the presence of undiagnosed disease of the chest. The presence of monilia in the sputum among individuals with chronic pulmonary disease is generally regarded as a common contaminant. However, contributors from Scandinavia ascribe some significance to this finding among sarcoidosis patients. (On speculative grounds, one might question the wisdom of using broad-spectrum antibiotics in patients demonstrating this degree of superimposed moniliasis). The observation of questionable vicarious menstruation and the subsequent development of cancer of the cervix are undoubtedly coincidental.

Case 2: A.L., a colored female, age 52, was admitted to the Lloyd Noland Hospital in Fairfield, Alabama, on January 27, 1952, because of shortness of breath. Apparently she had been well until approximately six weeks previously when she observed mild bilateral flank pain which radiated into both breasts. For approximately one week prior to admission she had fever ranging from 101 to 102 degrees F. daily. Shortness of breath became so severe that she required four pillows at night. She was seen in the clinic 10 days before admission with slight fever, tachycardia of 120 and respirations of 32 per minute. Examination of the chest disclosed a friction sound over the left lower lobe, moist rales and gross suppression of breath sounds over this area. An x-ray film of the chest at that time was interpreted as being consistent with cardiac decompensation (Figure 4). After three days of penicillin therapy, the temperature became normal, the pulse rate dropped to 88, but respirations remained 32 per minute. There was considerable improvement in her ability to breathe comfortably but four days later respiratory difficulty returned. When seen in the clinic at this time, respirations were 40 per minute, the friction sound had disappeared, rales and breath sound changes persisted, but it was now observed that the second pulmonic sound had become tympanitic.

There was some doubt as to whether an illness at age 10 had been correctly diagnosed as having been smallpox. She denied having had any illness whatsoever during the past five years. The family history, occupational history, history of

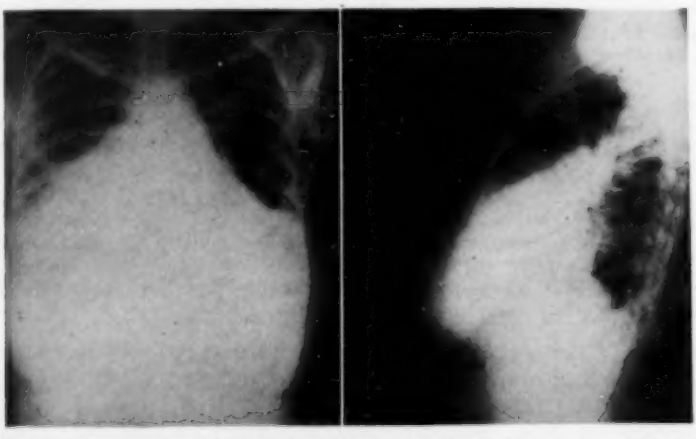

FIGURE 4: Demonstrates large bleb right apex, reticulated and nodular changes both lung fields, a triangular cardiovascular shadow and dense pneumonic infiltration in the right lower lung field. The right lateral film demonstrates that the pneumonic infiltration is almost completely confined to the limits of the right middle lobe.

exposure to tuberculosis and a review of systems disclosed no contributory information. She had noted no shortness of breath prior to the onset of the present illness.

The oral temperature was 99, the pulse rate varied from 96 to 112 and respirations were 32 per minute. The blood pressure was 108/70 and her weight was 127¼ pounds (significantly below her usual weight). She was a well developed but slightly undernourished patient lying flat on her back but obviously tachypneic. Sticky moist rales were found over both lower lung fields and in the axillae. The heart was thought to be enlarged and somewhat triangular in contour. The second pulmonic sound was tympanitic and greater than the second aortic sound. Although no murmurs were observed, an inconsistant pericardial friction sound was heard. The liver and spleen were not palpably enlarged, no significant glandular enlargement was detected and there was no edema.

Laboratory data disclosed no evidence of anemia; the leukocyte count and differential were normal with 5 per cent eosinophils; the urine was negative; the blood Kahn test was negative; the sedimentation rate was 27 mm./hour (Cutler); the blood urea nitrogen was 25 mg. per cent; a sickle cell preparation was negative; the venous pressure and circulation time were normal; the vital capacity was 1.2 liters (38 per cent); a 1:10,000 Mantoux test was negative and numerous sputum specimens for acid-fast bacilli were negative. An electrocardiogram made two days after admission was interpreted as follows: "Rate 125. Low voltage. Small Q1. Inverted T waves in limb lead and in V2, V4 and V6. Consistent with myocardial disease and suggests pericardial effusion."

During the hospital stay it was found that digitalization and mercurial diuretics were of no benefit. On the day before discharge an intermittent gallop was detected in the pulmonic area and an apical pericardial friction sound was heard by several observers. She was discharged on February 1, 1952, with the diagnosis of acute benign non-specific pericarditis with pulmonary parenchymal involvement. While under observation in the clinic she gained weight gradually. Tubular breath sounds became apparent over the right middle lobe. She was presented at Staff Conference on March 5, 1952, at which time the diagnosis of sarcoidosis was first seriously entertained because of our experience with Case 1. Further laboratory studies were carried out. A 1:1000 Mantoux test was negative, total proteins were 8.0 gm. per cent with serum albumin of 2.96, serum globulin of 5.04 and a rate of 1:1.7. From April 15th until June 20, 1952, she complained of cough productive of green sputum and some vague chest pain. Although she had consistently run a low grade fever there had been a 10 pound increase in her weight.

On June 20, 1952, she began having blood-streaked sputum which was followed by a large hemorrhage. She estimated that she lost a "quart of blood". She was readmitted to the Lloyd Noland Hospital the following day. On examination, the temperature was normal, the pulse rate was 80, respirations were 24 and the blood pressure was 120/80. No abnormality of the heart was detected. Coarse rales with a "to and fro cracking sound" were heard over the right middle lobe region and occasional moist rales were heard over both lower lung fields. The liver edge was palpated two fingerbreaths below the right costal margin. The spleen was not felt and there was no detectable adenopathy.

Laboratory studies disclosed sedimentation rate of 21 mm./hour (Cutler); numerous sputa for acid-fast bacilli on this admission were negative; the total proteins were 8.8 gm. per cent with albumin of 3.0, globulin of 5.8 and a ratio of 1:1.9.

On June 22nd, she had a series of massive pulmonary hemorrhages rapidly filling three large emesis basins. The bleeding continued for more than an hour during which time she lapsed into shock. A liter of blood was given intravenously, following which shock was controlled and no further bleeding occurred. She was discharged several days later to the surgical service of the Jefferson Hillman Hos-

pital for a supraclavicular tissue biopsy.[1] During the course of this procedure a node was found which was described pathologically as being consistent with sarcoid.

Discussion

These two cases appear to be of unusual interest because large pulmonary hemorrhages have rarely been observed among patients with proved sarcoidosis.

Riley reviewed 52 cases in the Bellevue Hospital series. There is reference to blood-streaked sputum in several instances, but no large pulmonary hemorrhage was observed.[2] Oblath and Farber studied 40 patients among whom four had small hemoptyses.[3] McCort et al., reported 28 cases of sarcoidosis among whom two had slight hemorrhages.[4] In all the reports where bleeding has occurred there has been no correlation with the type of pulmonary involevment as seen radiographically.

The only proved case of sarcoidosis with fatal pulmonary bleeding recorded in the literature is that of Fisch and Freireich.[5] Definite bronchial dilatation was found in this case. Israel has a case with fatal pulmonary bleeding who on necropsy was found to have emphysematous and bronchiectatic changes.[6] Freiman is of the opinion that large pulmonary bleeding among sarcoidosis patients is due to bronchiectatic changes.[7]

It is of passing interest that among 1,316 cases of pulmonary hemorrhage in one series, not one case was diagnosed as sarcoidosis.[8] Among 200 cases of hemoptysis reported from the Mayo Clinic only one was proved to have sarcoidosis, but there is no reference to the amount of bleeding or the character of x-ray findings.[9,10]

It would, therefore, appear that pulmonary bleeding of the magnitude observed in these two cases is, indeed, an unusual happening among patients with sarcoidosis. However, these patients exhibited pulmonary changes of the more unusual character seen in this disease. Perhaps more of these cases with large pulmonary hemorrhages due to sarcoidosis will come to light as clinicians become more generally aware that sarcoidosis is capable of producing fibrotic, bronchiectatic and emphysematous changes.

SUMMARY

Two cases of large pulmonary bleeding due to sarcoidosis are added to the literature. The occurrence of unusual pulmonary lesions in sarcoidosis and the relationship to hemoptysis are stressed.

RESUMEN

Se gragan a la literatura dos casos de gran hemorrhagia pulmonar debida a sarcoidosis. Se recalcan la ocurrencia de lesiones primarias pulmonares inusitadas y su relación con la hemoptisis.

RESUME

L'auteur rapporte deux observations de grosse hémorragie pulmonaire due à la maladis de Besnier-Boeck-Schaumann. Il insiste sur la survenue

de lésions pulmonaires inhabituelles dans cette affection et leur relation avec les hémoptysies.

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Cortisone Treatment of Sarcoidosis

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Until the introduction of cortisone, management of sarcoidosis was limited to supportive measures and was notoriously ineffective in controlling the incapacitating ocular and pulmonary lesions. In the past, Fowler's solution, x-ray, urethane, nitrogen mustard, calciferol and antibiotics have been found to be of no value in the treatment of this disease.

In 1950, Thorn et al. reported one case treated with ACTH with no response.[1] Sones and co-workers,[2] however, obtained marked improvement in two cases treated with cortisone. Their studies caused them to postulate that a relative adrenal insufficiency may be present in sarcoidosis, thus theorizing the better response to cortisone. At the time of writing, approximately 20 cases[2-5] of sarcoidosis treated with cortisone, with variable response, have appeared in the literature. We present the following case report as an addition to the literature:

This is a 25 year old negro airman admitted to the Wright-Patterson Air Force Base Hospital on June 19, 1952. He dated the onset of his present illness to sometime in January 1952, when he noted an insidious onset of small, indurated lesions of the skin about the ankles. He was ultimately hospitalized at Selfridge Air Force Base in May 1952, when there was a marked increase in the number of nodules with bilateral involvement of the lower legs. Also during this interval (from January to May) he noted photophobia, burning and lacrimation of the eyes with no associated visual disturbances. He observed easy fatigability, some loss of appetite, and a weight loss of approximately 15 pounds. He remarked that approximately two months prior to admission he noted for the first time some blood streaked sputum lasting for about two or three days. There was no recur-

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FIGURE 1

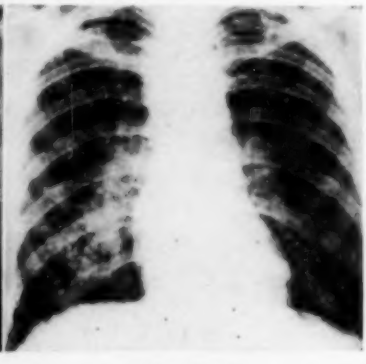

FIGURE 2

Figure 1: Before Cortisone Therapy.
Figure 2: Two weeks after Cortisone Therapy.

rence of this isolated incident. There has been some soreness of the anterior chest and substernally, made worse by movement. Skin biopsy from the right calf showed findings compatible with sarcoidosis. A chest x-ray film revealed bilateral enlargement of the hilar nodes with diffuse nodular infiltration throughout both lung fields. He was then transferred to this center for further evaluation and treatment.

Past History: Gonococcal urethritis in 1949 treated with penicillin; otherwise negative.

Family History: Also negative.

Physical Examination: At the time of admission to this hospital, the physical examination revealed a well-developed, well-nourished, colored male who appeared to be neither acutely nor chronically ill. Height 74 inches. Weight 184 pounds. Blood pressure 110/70. Pulse 80. Temperature 98.6 degrees F. No cervical lymphadenopathy. Chest was symmetrical with no limitation of motion. There was a decrease in the intensity of breath sounds uniformly over both lung fields. No other abnormalities were noted on auscultation or by percussion. Liver and spleen were not palpable. The skin of the thighs and legs were studded with multiple, solitary, indurated, non-tender reddish-brown nodules, too numerous to count (Figure 6). There was no palpable lymphadenopathy.

Laboratory Data: On admission to this hospital the hemoglobin was 15.1 grams per cent with 6,100 white cells—54 per cent of which were neutrophils, 34 per cent lymphocytes, 9 per cent monocytes, and 2 per cent eosinophils. Total protein 7.9 grams per cent with 5.3 grams per cent of albumin and 2.6 grams per cent of globulin. Blood calcium 10.2 mgms. per cent. Inorganic phosphorus 4.9 mgms. per cent. Acid phosphatase 1.1 units. Alkaline phosphatase 1.5 units. Repeat urinalyses were within normal limits. Sputum studies were negative for acid-fast bacilli and fungi. PPD first and second strength skin tests were negative. Histoplasmin: 4 plus. Coccidioidin: Negative. BSP showed no retention of dye in 45 minutes. Cephalin flocculation: 3 plus. Icteric index: 12.6. Thymol turbidity: 12 units. Cholesterol: 197 mgms per cent. Van den bergh, direct: Negative. Chest x-ray film (Figure 1) revealed evidence of fine nodular fibrosis throughout both lung fields. Multiple densities were present, together with bilateral enlargement of the hilar lymph nodes. Repeated corrected sedimentation rates during the course of hospitalization ranged from 35 mm./hr. to normal limits. Hemoglobin remained normal throughout hospitalization. Repeat serum protein on July 3, was 5.2 grams per cent of albumin, and 3 grams per cent of globulin. Repeat on

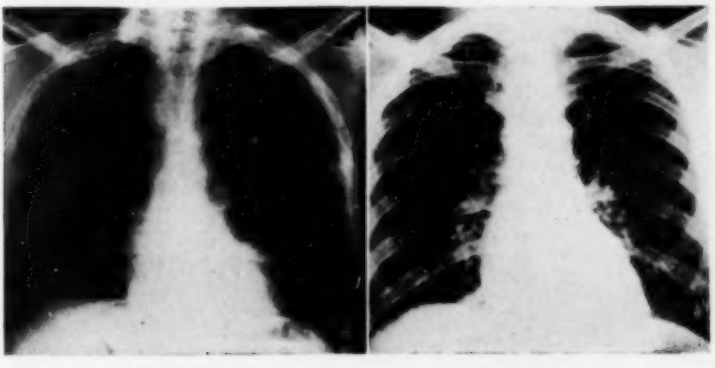

FIGURE 3 FIGURE 4

Figures 3 and 4: After Cortisone Therapy. Maximum clearance in Figure 3. Note increase in parenchymal lesions in Figure 4 (eight weeks after stopping Cortisone).

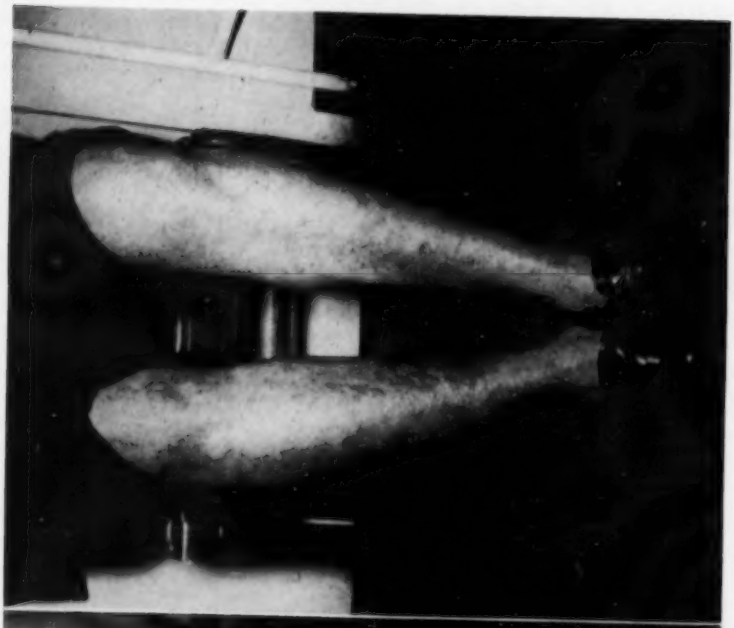

FIGURE 7: After Cortisone Therapy.

FIGURE 6: Before Cortisone Therapy.

November 10 showed 5.1 grams per cent of albumin and 3 grams per cent of globulin. Calcium was 11.3 mgms. per cent. Inorganic phosphorus 3.3 mgms. per cent. BUN 3.5 mgms. per cent. Maximum breathing capacity done in July on admission was 98.5 liters per minute.

Course During Hospitalization: Shortly after admission the patient was seen in consultation by the Eye Clinic because of complaints of slight burning, itching and photophobia. The consultant reported several small mutton-fat type "KP" areas on the endothelial surface of the corneas bilaterally. Except for small lace-like vitreous opacities, the vitreous was clear. It was his impression that the patient had uveitis, anterior, bilateral, granulomatous in type and compatible with the diagnosis of sarcoidosis. A biopsy of a skin nodule was done on July 11 and reported as compatible with sarcoidosis (Figure 5). During the course of pre-treatment observation, there was no evidence of fever or toxicity nor was any regression of the skin or lung lesions evident.

On August 7 he was started on cortisone receiving an average of 200 mg. daily. Within two weeks, the lesions on the legs began to fade and by September 11 they had completely disappeared (Figure 7). Also, at this time, the uveitis had completely resolved. Chest x-ray film of August 22 (after two weeks of cortisone) disclosed considerable parenchymal and hilar improvement (Figure 2). Cortisone was discontinued on September 11, 1952 after a total of 6 grams. Maximum improvement of the lung lesions was observed on the x-ray film of October 28 (Figure 3) though complete clearing did not occur. At the end of the period of treatment he had no complaints, felt very well, and had gained eight to 10 pounds.

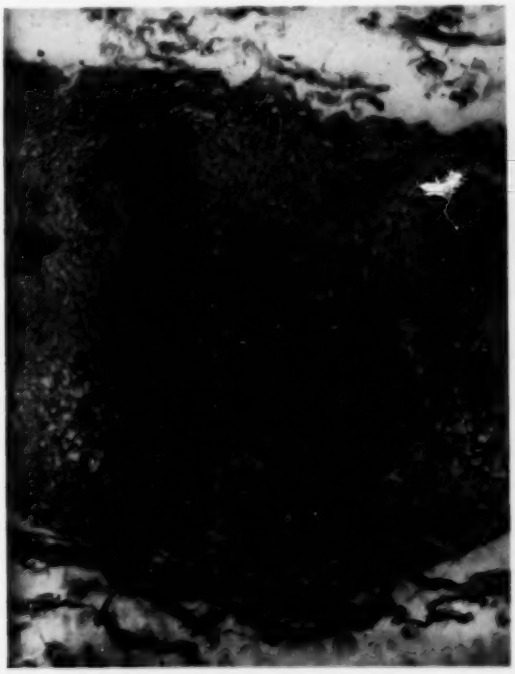

FIGURE 5: Section of skin taken to show a non-caseating epithelioid granuloma characteristic of other lesions in the subcutaneous tissue. A Langhan's type "giant cell" is to be seen in the lower portion of the field (and another at 2 o'clock). Compatible with sarcoidosis.

Maximum breathing capacity determined in November was 109.2 liters per minute as compared with the base line of 98.5 liters per minute. A repeat chest x-ray film in November, eight weeks after cortisone therapy had been stopped (Figure 4), showed a slight increase in the diffuse nodular infiltration of both lung fields as well as persistence of bilateral hilar lymphadenopathy. No eye or skin recurrences have appeared to date. Comparison of original and repeated electrolyte studies revealed no changes secondary to cortisone therapy.

SUMMARY

A case of sarcoidosis with involvement of the eyes, the skin and lungs, treated with cortisone, is presented. Complete resolution of the uveitis and skin nodules occurred. The chest x-ray film revealed marked parenchymal and moderate hilar lymphadenopathy resolution, though complete clearing never was achieved. Eight weeks after completion of steroid therapy, an increase of parenchymal lesions was noted. These results compare with similar recent reports in the literature.

RESUMEN

Se presenta un caso de sarcoidosis con compromisa de los ojos, la piel, y los pulmones, habiéndose tratado con cortisona. Se obtuvo la completa resolución de la uveitis y de los nódulos cutáneos. La película a los rayos X mostró resolución marcada del parénquima y moderada resolución de la linfadenopatía hiliar, aunque completo aclaramiento nunca se logró. Ocho semanas después de terminado el tratamiento con esteroides, se notó un aumento de las lesiones parenquimatosas. Los resultados son comparables a los similares referidos en la literatura.

RESUME

Les auteurs rapportent un cas de maladie de Besnier-Boeck-Schaumann, avec atteinte des yeux, des téguments, des poumons, qui a été traitée par la cortisone. Il y eut une disparition complète de l'uvéite, et des nodules cutanés. La radiographie montre une amélioration importante de l'atteinte parenchymateuse, et une action plus discrète sur les adénopathies hilaires. Toutefois, il n'y eut jamais un nettoyage complet.

Huit semaines après que le traitement ait été complété par l'action des stéroïdes, on constata un accroissement des lésions parenchymateuses. Les auteurs comparent ces résultats avec les observations récemment rapportées dans la littérature.

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Pneumomediastinum in the Newborn: A Report of Three Cases

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In the past few decades, a great deal has been learned concerning the newborn who is dyspneic and in respiratory and circulatory distress. Great emphasis has been placed on trauma to the head occurring during parturition. Clogging of the respiratory passages and resultant atelectasis is a well known cause. Aspiration of amniotic fluid with formation of an amniotic membrane is occasionally found. Failure of the lungs to expand normally is a common factor in embarrassment of respiration and circulation. Certainly the majority of cases of respiratory and circulatory difficulty in the newborn are due to trauma or to atelectasis.

Occasionally congenital defects of the broncho-pulmonary system or the cardiovascular system will be at fault. There are reports of congenital cysts of the lung, congenital duplications of the esophagus, agenesis of a lung, tracheo-esophageal fistula, absence of the diaphragm or a portion thereof, and other unusual conditions leading to extreme distress in the newborn.

Recently, in three newborns, we have encountered respiratory and circulatory difficulty caused by pneumomediastinum and pneumothorax. All of these cases have improved spontaneously with conservative treatment.

Case 1: This infant was delivered at the St. Joseph Hospital on January 12, 1952. It apparently was normal at birth. The first stage of labor lasted eight hours, the second stage one hour, and the third stage 20 minutes. It was necessary to administer artificial respiration and oxygen under pressure to initiate breathing. Respirations were labored, the child was cyanotic, and breathed noisily. On the first day, it vomited some black material resembling blood. The following day, it was still necessary to continue oxygen because of the extreme cyanosis. On the third day of life, cyanosis was less and x-ray films disclosed mediastinal emphysema (Figures 1A and 1B). By the fourth day it was possible to discontinue the administration of nasal oxygen and respirations had returned to normal. On the fifth day, x-ray films disclosed almost no air in the anterior mediastinum (Figures 2A and 2B). It made an uneventful recovery and was dismissed on the eighth day of life, having regained its normal birth weight.

Case 2: This was a white female child born in St. Joseph Hospital in Fort Wayne, Indiana, on September 13, 1952, after an uneventful labor. The mother had had one previous normal child. Demerol had been administered sparingly during the labor, and drop ether was given the mother during the second stage of labor which lasted 18 minutes. The baby did not breathe spontaneously and was placed in an airlock. It was in the airlock for 12 hours and was given alpha lobeline, and caffein sodium benzoate but remained listless and became cyanotic when removed from the airlock. At this time, physical examination revealed mediastinal crackles. A chest x-ray films disclosed air in the anterior mediastinum (Figures 3A and 3B). The child was closely observed and given nasal oxygen. It remained slightly cyanotic for two days but gradually the respirations became progressively less

grunting, the color improved, and at about this time left pneumothorax became evident (Figures 4A and 4B). Since the child was improving spontaneously, it was not necessary to tap the chest. Recovery was rapid and the child left the hospital on the seventh day of life, clinically well.

Case 3: This was a male infant weighing seven pounds and two ounces, born at the Fort Wayne Lutheran Hospital, January 20, 1953. About an hour and a half after delivery, the infant was noted to be cyanotic and respirations were rapid and grunting in character. Auscultation of the chest disclosed bronchial type respirations but no rales. He was placed in an oxygen tent with immediate improvement. The following day, a lateral x-ray of the chest disclosed air in the anterior medias-

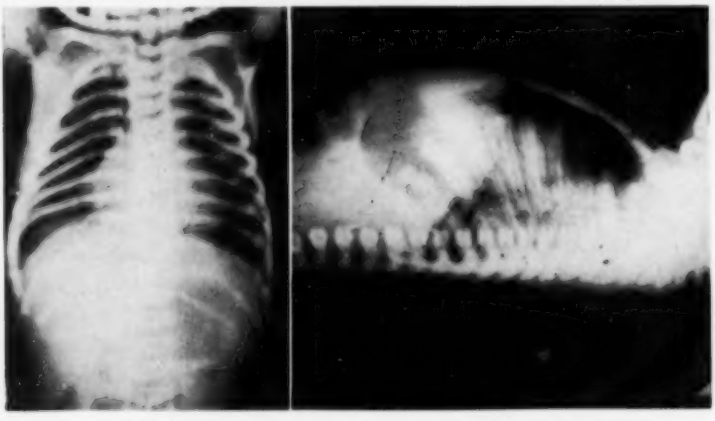

FIGURE 1A FIGURE 1B

Figure 1A: AP of chest at birth showing nothing remarkable.—*Figure 1B:* Lateral of chest showing the large amount of air in the anterior mediastinum.

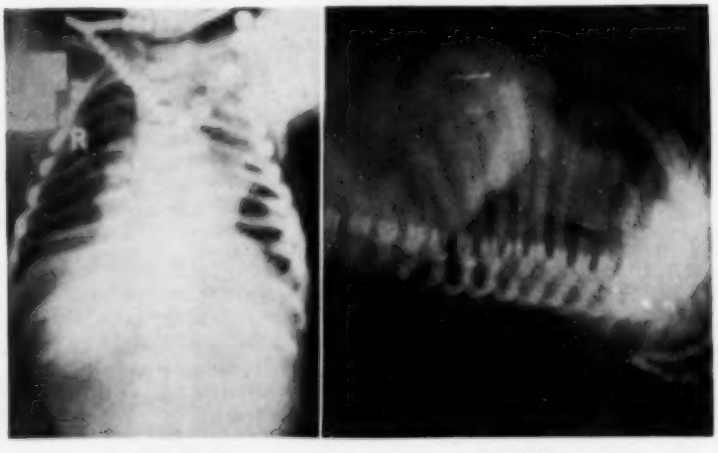

FIGURE 2A FIGURE 2B

Figure 2A: AP of chest disclosing a small left pneumothorax.—*Figure 2B:* Lateral of chest showing much less air in the anterior mediastinum.

tinum. Respirations were still rapid and grunting in character. Two days later, the baby appeared normal and did not require further therapy. He was dismissed on the sixth day of life.

Historical:

Pneumomediastinum, or airlock, was first called to attention by Guillot[3] in 1853. He presented two cases of mediastinal emphysema, discovered at post mortem examination. Since then, there have been occasional reports of its occurrence, and in 1940, DeCosta,[1] in a review of the world literature, found reports of 46 cases that had occurred in infants up to the age of 10 days. In 21 other reports, the children were over 10 days of age and in the early months of life. This latter group he attributed largely to congenital anomalies and inflammatory conditions.

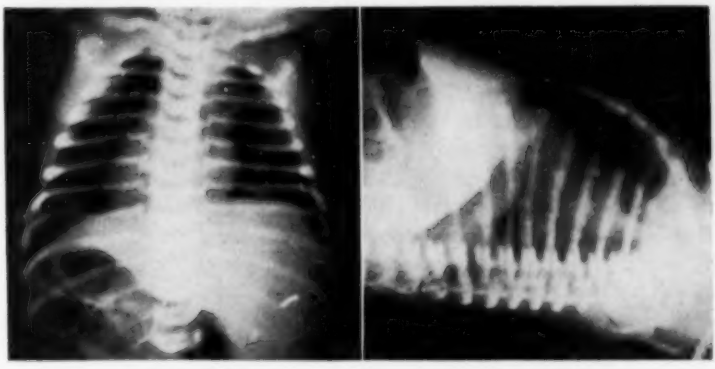

FIGURE 3A FIGURE 3B

Figure 3A: AP of chest showing nothing remarkable.—*Figure 3B:* Lateral of chest showing great quantity of air in the anterior mediastinum.

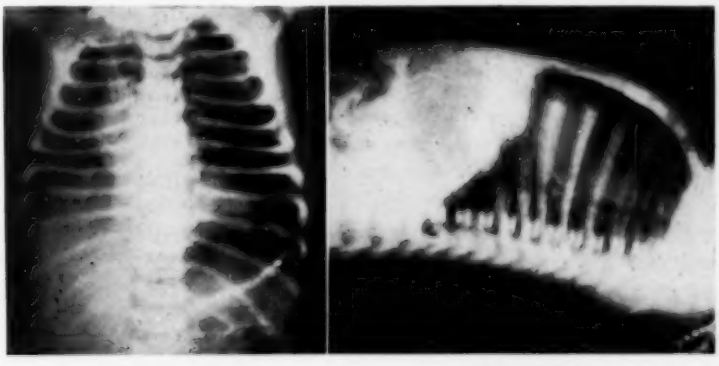

FIGURE 4A FIGURE 4B

Figure 4A: AP of chest showing a well developed pneumothorax and compression and crowding of the great vessels of the superior mediastinum to the right.—*Figure 4B:* Lateral of chest showing a decrease in the air in the anterior mediastinum.

Etiology:

Pneumomediastinum may be caused by a number of conditions.[8] Chest surgeons are quite familiar with post surgical and post traumatic pleural leaks with subcutaneous and mediastinal emphysema. Perforating wounds of the larynx, trachea, and bronchi may be accompanied by this condition. Perforating wounds of the diaphragm or the neck may admit air into the mediastinum. This thus may be a complication of head and neck surgery. Rupture of the esophagus is almost always complicated by mediastinitis with air. There have been a few cases following pneumoperitoneum.

When pneumomediastinum occurs in the newborn, it is most commonly due to congenital anomalies of the tracheo-bronchial tree or to excessive intra-alveolar pressure during attempts at resuscitation. Infection is generally not a factor in the newborn but in older children it may be a cause. Some cases apparently occur spontaneously and are never adequately explained. Such is illustrated by the third case.

Pathology:

Air is classically found in the anterior mediastinum and is best shown by lateral x-ray film. The studies of Macklin[6] and Fisher have been largely responsible for our understanding of the phenomonen. They showed that if alveoli are over-distended and alveolar rupture occurs, air can be forced along the extra-alveolar pulmonary vessels to the root of the lung. These vessels, being extrapleural structures, provide a direct pathway to the mediastinum. The air thus collects in the anterior mediastinum.

If the pressure in the anterior mediastinum is great enough, the air may rupture the mediastinal pleura and leak into the pleural cavity and produce pneumothorax. The other theory concerning the pathogenesis of pneumothorax is that it may come from a laceration of the surface of the lung. This is probably seldom the case for DeCosta[1] was unable to cause leakage through the visceral pleura with pressures of 100 millimeters of mercury whereas in the mediastinum, a pressure much less than this would regularly cause a rupture of the mediastinal pleura.

Should infection be conveyed from the ruptured alveoli, it would theoretically be possible for an inflammatory process of the lung to be initiated.

Symptomatology:

After considering the pathology of pneumomediastinum, the symptomatology is easily understood. The signs vary, depending on the degree of the process. Slight dyspnea may be the only sign, and it may easily pass for mild atelectasis. As the quantity of air becomes greater, marked interference with respiration may ensue. Cyanosis, rapid grunting respirations, and distention of the great veins of the neck will be evident. The presence of air in the mediastinum under pressure may be great enough to cause the above symptoms. In addition, air compressing numerous tiny pulmonary arterioles and venules may interfere with pulmonary circulation. If there is accompanying pneumothorax, additional interference with cardiopulmonary function may ensue. On the other hand, if there is a great degree

of mediastinal emphysema, and the mediastinal pleura ruptures with consequent pneumothorax, the symptoms may become milder because of release of the increased mediastinal pressure. If the air continues to be pumped from the alveoli into the mediastinum, symptoms will become worse unless prompt treatment is undertaken.

Diagnosis:

A high index of suspicion in all cases of respiratory and circulatory difficulty in the newborn is the first step toward a correct diagnosis. Frequently, a history of difficult resuscitation is obtained. It may not be present however, as is illustrated by case 3. A crackling sound in the mediastinum is almost diagnostic. In exceptional cases, air may be noted in the suprasternal notch. Real proof is forthcoming on lateral x-ray film inspection. Gumbiner and Cutler[4] have emphasized the value of chest x-ray films in illustrating this. Even though the anterior-posterior x-ray film fails to disclose an abnormality, one ought to resort to a lateral ray, for the air is more easily seen in the anterior mediastinum under such a view.

Apparently, pneumomediastinum is not so rare as one would be led to believe by the sparsity of reports in the literature. Davis and Stevens[3] found six cases of pneumothorax in the routine roentgenographic examination of 702 consecutive newborns. If pneumomediastinum precedes pneumothorax in such cases, the incidence of mediastinal emphysema of more than 1 per cent is probably a fact for not all cases of pneumomediastinum will produce pneumothorax.

Treatment:

Oxygen by mask or funnel is of great value in tiding the infant over the acute phase of circulatory and respiratory embarrassment. In many cases, symptoms are so mild that no treatment is necessary. If symptoms are increasing in severity, it is imperative to control the source of air. One should avoid applying positive pressure to the infant for fear of forcing more air into the mediastinum.

Should symptoms warrant, one must provide an outlet for the accumulated air. One may drain the anterior mediastinum through the third left intercostal space,[4-7] directing the needle medially until the air is reached and the tension released. If one is not able to release the air by means of a needle, a small incision at the suprasternal notch will provide an air outlet. If pneumothorax is marked, an intercostal catheter connected to negative suction, will provide for egress of air and allow the lung to expand.

A note of thanks is extended to Dt. Wallace Bash and to Dr. C. Wm. Goebel for permitting us to publish these cases.

SUMMARY

1) Three cases of mediastinal emphysema in the newborn have been presented.

2) A brief discussion of the etiology, historical background, symptomatology, pathology, diagnosis, and treatment has been given.

RESUMEN

1) Se presentan tres casos de enfisema mediastinal en el reciennacido.

2) Se discuten brevemente la etiología, los antecedentes históricos, la sintomatología, la anatomía patológica, y el diagnóstico y tratamiento.

RESUME

1) Les auteurs présentent trois cas d'emphysème médiastinal du nouveau-né.

2) Ils donnent une revue rapide de l'étiologie, l'historique, la symptomatologie, l'anatomie pathologique, le diagnostic et le traitement.

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Broncholithiasis

Report of a Case Occurring in Active Pulmonary Tuberculosis

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Standard medical texts omit the subject of broncholithiasis completely or merely acknowledge its existence. One must turn to the periodic literature to obtain detailed information. In view of the foregoing, it seems appropriate to briefly review the literature incident to reporting an additional case of broncholithiasis as occurring in the presence of active pulmonary tuberculosis.

Incidence: Although scattered references to broncholithiasis have appeared for hundreds of years, it is only since the latter part of the 19th century that the subject has attained any prominence, emphasis being most marked in the past decade. In 1941 Van Ordstrand[9] discovered 30 theretofore reported cases incident to reporting two additional cases. By 1946 Zahn[10] reporting on the one case of broncholithiasis discovered among more than 4,000 tuberculous patients stated that 71 cases had been reported prior to that time. In 1948 Freedman and Billings[2] added seven cases to the 96 reported in the literature. Schmidt et al.[7] in 1949 presented a masterful paper in which were reported 13 new cases. Since that time the Anglo-American literature, in articles and discussions thereof, has contained references which increase the number of cases of broncholithiasis reported therein to 142.[3-5,11]

Etiology: One may broadly classify broncholiths into two groups in accordance with their site of origin.

(a) Extrinsic calculi are those arising from aspirated foreign bodies including tissues, secretions and dusts and are formed within the bronchial lumen—a rare occurrence.

(b) Intrinsic calculi take their origin within the tissues proper of the lung, bronchi and lymph nodes and may be subdivided as follows:

(1) Senile calcifications of the elastic cartilage of the bronchi is a function of aging. Sequestration results in bronchial calculi.

(2) Metastatic calcification consists in the deposition of calcium in soft tissues incident to hyperparathyroidism, multiple myeloma, renal rickets, etc. Since the thoracic examples of this type of calcification occur peripherally and rarely, they do not often result in broncholithiasis.

(3) Dystrophic calcification is the deposition of calcium in necrotic, inflamed or degenerated tissue and constitutes the most common mechanism responsible for the occurrence of broncholithiasis.

Pathology: The mechanisms underlying the above have never been definately established although general and local hypercalcemia, local changes in pH and toxic or idiopathic factors have been cited. By whatever process

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it occurs, broncholith formation results in an end product whose chemical composition is similar to that of bone. The main constituents of stones are calcium carbonate and calcium phosphate in essentially the ratio existing in bone. The factors which precipitate the migration of the calcifications are unknown although Head and Moen[3] have suggested that the cause is nontuberculous infection. Auerbach[1] suggests erosion of the bronchial wall as a result of continuous respiratory movements.

The stones are irregular, gray-white and of a few millimeters in dimensions (pigmentation, particularly secondary to anthracosis, occurs). They usually occur in the right lung and particularly in association with the right upper lobe. Schmidt[7] attributes this to the greater number of lymph nodes on the right, especially numerous in the region of the upper lobe bronchus.

Symptoms: The pathognomonic symptom of broncholithiasis is the expectoration of a stone. There is no characteristic clinical picture. At one extreme is the patient who is discovered at autopsy to have bronchial calculi although known to have been symptom free during life. At the other is the patient who constitutes a medical emergency because of chest pain or hemoptysis. One need only recall that broncholiths are foreign bodies to predict the symptoms they can cause.

Cough is an almost universal symptom. At first dry and hacking, it becomes productive of mucoid material in increasing amounts as bronchial irritation mounts. With partial obstruction and infection, the sputum becomes purulent.

Hemoptysis occurs in most cases, usually to a minimal degree. On occasion, transfusion or surgery may be indicated.

Pain was present in approximately one-half of all reported cases. It is usually retrosternal and of a pleuritic or tearing nature.

Fever, chills, weight loss, wheezing, dyspnea and other symptoms indicative of pneumonitis, abscess, bronchiectasis, atelectasis and empyema have been reported.

Physical Findings: The only abnormal physical findings are those arising directly or indirectly from hemorrhage or bronchial obstruction. Anything from a wheeze to atelectasis may be noted.

Roentgenography: Calcification in the tracheobronchial lymph nodes or in the lung fields proper is the usual roentgenographic picture. Secondary complications will be accompanied by their characteristic roentgenographic changes. Laminography may be of value. Schmidt[7] has called attention to the triangular area of pulmonary collapse at whose centrally located apex is noted an area of calcification.

Bronchoscopy: Because of the presenting clinical picture, most patients with symptomatic bronchial calculi are subjected to bronchoscopy. The endoscopist usually discovers ulceration or granulation tissue, frequently with the calculus buried within the tissue. The involved area may be inaccessible and thoracotomy necessary. Nevertheless, bronchoscopy remains a valuable diagnostic procedure.

Treatment: In many of the cases the broncholiths are spontaneously

evacuated, removed by endoscopy or expectorated after instrumentation and dilatation. A few cases must be treated surgically because of existing complications. Finally, because of the laudible increase in exploratory thoracotomies in those cases in which an obscure lesion is noted, it is anticipated that more bronchial calculi will be uncovered and treated in this fashion. Since the underlying pathology fosters recurrence, it is advisable to leave as much functioning lung tissue as possible. Appropriate medical therapy is administered when indicated for the secondary complications.

Case Report: This 58 year old male fisherman was admitted to the hospital on March 31, 1952, with the roentgenographic and bacteriologic diagnosis of pulmonary tuberculosis, active. He gave a history of hospitalization from 1936 to 1942 because of pulmonary tuberculosis for which he was treated with bed rest and phrenicotripsy. Subsequent to this initial hospitalization he worked full time at his trade, remaining asymptomatic until the summer of 1951 when he noted the gradual onset of weight loss, weakness, easy fatigability, cough, hemoptysis and night sweats. Although evaluation in January of 1952 revealed the presence of active pulmonary tuberculosis, he deferred hospitalization until March 31 of that year.

Physical examination on admission revealed a thin male who appeared chronically ill. Temperature was 97.6 degrees F. The pulse was 100. The blood pressure was 140 mm. Hg. systolic and 100 mm. Hg. diastolic. Height was six feet. Weight was 145 pounds. With the exception of a long-standing neurodermatitis, the abnormal physical findings were limited to the chest. There was noted a visible and palpable lag of the left hemithorax with increased vocal fremitus and bronchial breathing over the left subapical region posteriorly.

Roentgenogram of the chest revealed an extensive exudative lesion in the left upper lobe with cavitation. Numerous calcifications were noted in the lung fields and mediastinum adjoining the left hilus. The sputum contained many tubercle bacilli on direct smear and culture.

Subsequent to admission the patient was placed on strict bed rest. Para-aminosalicylic acid was started at a dosage of 12 Gm. per day. However, because of gastrointestinal symptoms, the latter was reduced to approximately 8 Gm. per day. Because of persistence of symptoms which prompted admission, he was given 1 Gm. of streptomycin per day for 10 days. There immediately followed notable clinical improvement. Subsequent thereto 1 Gm. of streptomycin three times per week was given. Under the described regimen he exhibited definite limited clinical improvement. Bronchoscopy revealed only the presence of yellow mucopurulent material in the left upper lobe bronchus. Bronchography failed to reveal definite evidence of bronchiectasis. In December 1952 he was subjected to pneumonectomy and later to thoracoplasty. The former procedure was, technically speaking, extremely difficult. Examination of the mediastinum during surgery failed to reveal any abnormality in number or character of the lymph nodes.

Two months after admission to the hospital he casually mentioned the expectoration of a stone which he presented to the examiner. This was grayish white, irregular and of several millimeters in dimensions. Its consistency was of bone. Questioning revealed that between January and March 1952 on three occasions he expectorated a stone. Each episode began with an increase in the frequency and severity of the already present cough as well as increased expectoration of mucopurulent material. At no time was there hemoptysis, pain nor other attendant symptoms of any sort.

Pathologic examination of the removed lung revealed fibrocaseous tuberculosis with multiple cavitation. Search was specifically made for broncholiths and sources thereof. None was found. He is making an uneventful recovery from surgery.

Discussion

Broncholiths most commonly arise within intrathoracic tissues previously infected with tubercle bacilli. Surprisingly, their appearance during active pulmonary tuberculosis has been noted infrequently. Stivelman[8] reported one case in 5,000 active tuberculars while Zahn[10] noted a single case among 4,000 such patients. Pritchard[6] reported two cases in 7,000 patients with tuberculosis. Since many tuberculous patients with active disease have had previous episodes of activity, one would expect a high incidence of broncholithiasis in them. Moreover, they are susceptible to secondary infection which Head[3] contends precipitates the migration of stones. In all probability, such an increased incidence of broncholithiasis exists in active tuberculosis but has not been reported. More frequent direct questioning of patients with regard to the expectoration of stones should confirm this as should future reports in the literature.

SUMMARY

Broncholithiasis has been discussed and the literature briefly reviewed. A case of broncholithiasis occurring in active tuberculosis is reported. It is suggested that the incidence of such cases is greater than recorded. More frequently the patient should be specifically queried regarding this phenomenon.

RESUMEN

Brevemente se revist la literatura y se discute la broncholitiasis. Se refiere un caso de broncholitiasis que ocurrió en tuberculosis activa. Se sugiere que incidencia de tales casos es mayor de lo que se ha referido. Debe ser investigad o mas frecuentemente el enfermo en relación con esta posibilidad.

RESUME

L'auteur met en discussion un syndrome de broncho-lithiase et passe en revue rapidement la littérature concernant ce sujet. Il rapporte une observation de broncho-lithiase survenue au cours d'une tuberculose évolutive. Il lui semble que la possibilité de tels cas est plus importante qu'on ne le rapporte habituellement. On devrait plus souvent rechercher ce phénomène par l'interrogatoire des malades.

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Training in Cardiology

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The evergrowing ramification of present day medical specialization though it has raised the quality of medical care, has also produced men who "know more and more about less and less." The field of heart and circulation alone nowadays requires subspecialists in peripheral vascular disease, in hypertension, in congenital heart disease, in pediatric cardiology; it has produced electrocardiographers, vectorcardiographers, ballistocardiographers, hemodynamic clinicians, electrolyte and renal physiologists. It is a rare institution indeed where, in cardiology alone, an attempt is made to provide the proper balance of all forces and it is a rarer person yet whose vision has escaped this specialistic myopism in cardiology. If he has, he is generally frowned upon as a jack of all trades who would have done better to continue his earlier studies on the left atrial electrocardiogram. This trend toward specialism and subspecialism is not confined, of course, to this field but is general. It has its origin in the ever expanding horizon of medical knowledge. Almost by necessity the present requirements of medical knowledge leave the student graduating from medical school in a bewildered state of half education and with his training largely incomplete.

Postgraduate instruction in cardiology, therefore, begins with graduation from medical school. Even at best little more has been accomplished during the preceding four years than to teach the techniques of examination and the significance of history taking and of physical signs. There has been some integration of laboratory procedures with a general tendency of overevaluation of the latter with respect to the former both by the teacher and by the student. The training in basic medical science has largely been forgotten and rightly there has been little emphasis on treatment at this time.

The first step in postgraduate training is achieved during the internship. In this connection, a rotating internship of 12 months particularly in a private hospital is often of no value since it provides little more and often less than an undergraduate clerkship. Rotating internships in large charity institutions, on the other hand, are generally more rewarding because of the considerable responsibilities usually placed upon the ward physician and his frequent need for independent decisions. A straight 12 months internship in medicine is to be preferred, if possible at a teaching hospital, because it lays the background for medical experience and because it teaches practical therapy based on fundamental physiologic and biochemical prin-

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ciples. Teaching the "Art of medicine" can be learned on the ward as well and as effectively as in a private room, and the clinical aspects of heart disease and bedside diagnostic techniques can be refined and enlarged by conscientious visiting staffmen to an equal or better degree than by the overburdened and hurried practicing physician.

The second step consists of acquainting the budding internist who by now has advanced to an assistant residency with the special procedures in the diagnosis of cardiovascular disorders. By now, he has had some exposure to cardiac radiology, electrocardiography and to a catheterization laboratory, to name the most important tools. The practice of attending short intensive courses in special subjects (such as electrocardiography) is to be discouraged except as a refresher for the already experienced since even the best of these are quite ineffective on any level and often lull the participant into a false sense of security. After some exposure to these techniques during the assistant residency, one full year spent in a cardiovascular laboratory as an active member of the team will usually provide an adequate background if the laboratory can offer experience in all major fields of cardiology, and if the instruction stresses basic physiological principles. If such a laboratory is directed on a strictly clinical level, additional training in a department of physiology, biophysics or perhaps pharmacology becomes essential. As a rough guide, six months should be spent in what might be termed applied electrophysiology, and six months in the pursuit of hemodynamic studies. In order to obtain a balanced training period, it is important that the student maintain a continuous contact with general medicine throughout this year, by working one or two half days in a general medical clinic, by attending lectures and seminars on a variety of clinical and preclinical subjects, not concerned with cardiology, and whenever possible by actively participating in medical ward teaching. Further clinical bedside experience usually comes as the natural consequence by contact with the senior men of this specialty group.

At the end of this year such a fellow has just become a useful member of the unit and more likely than not he will be asked to continue. If he does, he must try his hand in active independent investigative pursuits, and now the machinery is set in motion which will test him as a future clinical research worker. He often decides, however, to return to another year of medical residency and then he takes the "plunge" into practice.

The third phase continues for the rest of his life in a permanent struggle to keep abreast of the ever changing aspects of the field. Reading a journal is out of fashion and very few practicing cardiologists take the leisure to even digest the journals of their own special field of interest. Since time is short he is best advised to read one journal well, and this should be one devoted to internal medicine. Important advances of lasting value will sooner or later find their way into this channel.

Once or twice a year he should attend a formal course or a formal meeting. Such events generally feature formal lectures or "papers," round table discussions, and occasionally practice or laboratory sessions. Of these, the formal papers are usually least instructive unless they are presented by

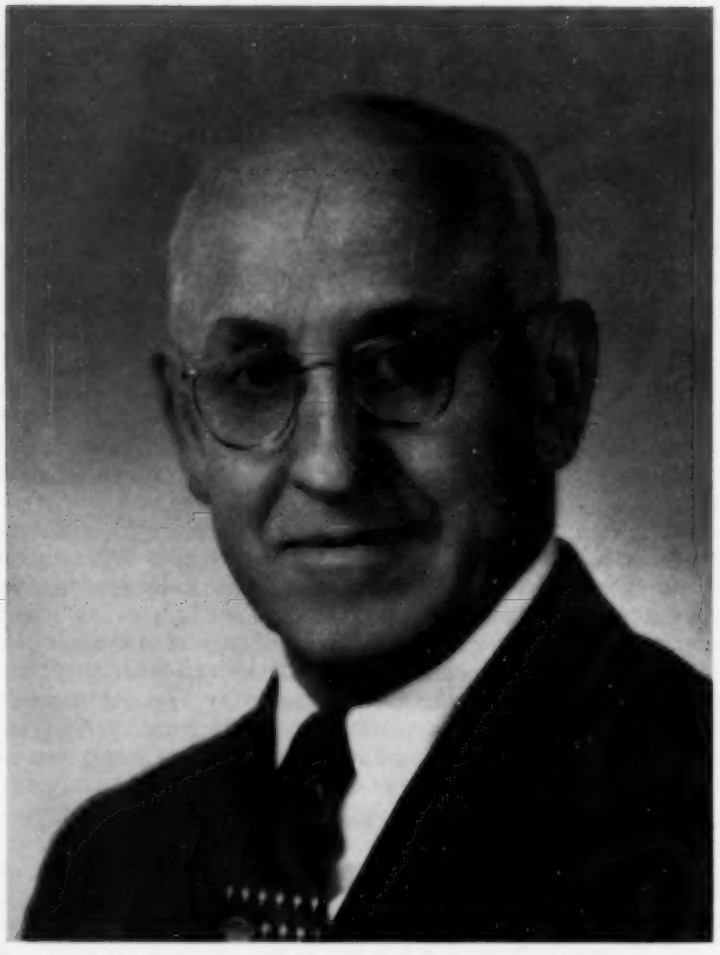
skillful "professional" teachers. They are likely to be monotonous and are confined to one man's view. On the other hand, round table discussions—often with question and answer periods—are generally more rewarding, since a topic can be viewed from all angles. This usually results in a satisfactory condensation of the present day knowledge concerning the subject of the discussion, particularly if the participants are chosen from a variety of disciplines. Such periods should be long, to allow for all possible contingencies and they are only effective if all members of the panel clearly understand the subjects and the ramifications that are to be covered. Frequent interplay among the discussors themselves or with discussors in the audience is desirable. Too frequently, such meetings bog down in irrelevant details, the result of poor planning. With audience participation such sessions can be far more instructive than formal presentations occupying a similar block of time.

The specialists who really desire information concerning present day investigative activities should not look to college meetings but should attend the fall or winter session of the Western, Southern, or Central Societies for Clinical Investigation, or to the spring meetings of the American Society for Clinical Investigation and the American Association of Physicians, all of which are open to everyone. Here the results of up to date clinical and experimental research are being presented in short presentations which in general are far more original and rewarding than formal, often already second hand orations at various college meetings. The ultimate of detailed specialistic information is available at the annual meeting of the Federation of American Societies for Experimental Biology ("Federation Meetings"), or the fall meeting of their component societies (Physiological Society, Society for Experimental Therapeutics, etc.).

In summary, postgraduate training in cardiology should focus on (a) a year or two of full time training in a cardiovascular laboratory, equipped to provide instruction in applied electrophysiology, (b) postgraduate course work with emphasis on round table discussion, (c) short intensive training sessions in small groups, covering a subject completely by lecture-demonstration and by practice.

WILLIAM ANDREW HUDSON, M.D.

PRESIDENT
AMERICAN COLLEGE OF CHEST PHYSICIANS
1954 - 1955



Dr. Hudson, born in Jasper, Arkansas, February 23, 1891, received his preliminary education at the public schools in Newton County, Arkansas and graduated from high school at Sedalia, Missouri. He entered Washington University, St. Louis, Missouri where he received his Bachelor of Science Degree (1918), Doctor of Medicine Degree (1920), and Master of Science Degree in Medicine in 1922. Dr. Hudson served as Interne and Resident at the Royal Victoria Hospital in Montreal, Canada on the service of Dr. Edward Archibald. He came to Detroit in 1923 as a member of the staff of the Henry Ford Hospital (with Dr. Roy McClure) and served on the teaching staff of the Ford Hospital School of Nursing. He took special courses at Trudeau School, Saranac Lake, the Chevalier Jackson

Course at Philadelphia, and made a tour of European Clinics during the 1920's.

He entered the private practice of thoracic surgery including endoscopy in 1925, being one of the first to limit his practice thereby setting thoracic surgery apart from general surgery and emphasizing it as a specialty. Dr. Hudson organized one of the first clinics for thoracic surgery in the State of Michigan at the Grace Hospital in Detroit heading the department as Chief of the Division of Thoracic Surgery from 1925 to 1951 (Retired) and continues as a consultant in thoracic surgery. From the beginning, he and Mrs. Hudson, who is a registered nurse, have worked together as a team in the operating room and at medical meetings throughout the world, he in the surgical aspect and she in the study of nursing principles of which she has been an active teacher.

Among his other hospital affiliations he is Chief Surgeon at Oakland County Tuberculosis Sanatorium, Pontiac, Michigan; Attending Surgeon, Head of the Department of Surgery at the Chest and General Hospital of Detroit (formerly the Detroit Tuberculosis Sanatorium); Consultant in Thoracic Surgery at North End Clinic, Wayne County General Hospital, on the Courtesy Staff of the Henry Ford Hospital, and a number of other institutions.

His past and present teaching experience and affiliations include grade school, Newton County, Arkansas; State Teachers Normal, Emporia, Kansas; Assistant and Instructor in Bacteriology and Pathology at Washington University, St. Louis; Associate Professor of Clinical Surgery at Detroit College of Medicine and Surgery and Wayne University School of Medicine (retiring 1946); Extramural Lectures at the University of Michigan School of Medicine; and lectures on thoracic surgery including endoscopy to the student nurses of Grace Hospital, Detroit.

Dr. Hudson has been associated with the American College of Chest Physicians as a Fellow and member of the Board of Regents since its very early days. He presided as the permanent chairman of the scientific section at both the First International Congress on Diseases of the Chest in Rome, Italy, in 1950 and at the Second International Congress on Diseases of the Chest in Rio de Janeiro, Brazil, in 1952. He holds honorary memberships in the St. Louis Medical Society and Sociedad Peruana de Tisiologia (Lima, Peru); Miembro Adherent, Sociedad Argentina de Cirugia Toracica (Buenos Aires). He delivered the 2nd Howard Lilienthal Memorial Lecture of the New York State Chapter, and the 1st Charles M. Hendricks Memorial Lecture of the Texas Chapter of the College.

He is a member of the Board of Directors of the Common Cold Foundation and other memberships in medical societies include the American Medical Association, Michigan State Medical Society, Wayne County Medical Society, Michigan Trudeau Society, Michigan State and National Tuberculosis Associations; Detroit Academy of Surgery; a Fellow of the American College of Surgeons, the American Association for Thoracic Surgery and the American Bronchoesophagological Society. A Founder-Member of American Board of Thoracic Surgery (Certified); the American Board of Surgery (Certified); and the International Bronchoesophagological Society.

Non-Medical memberships include the Christian Church, Rotary International, Detroit Board of Commerce, Detroit Yacht Club, City Farmers Club of Detroit, Save the Children Federation (Board of Directors, National Organization); a member of the advisory Council U. S. Department of Agriculture, South Forest Experimental R-SS Research Program; and the Northwest Pasture Improvement Group, Arkansas (Founder Member). He is a member of all York Rite Bodies and the Scottish Rite Bodies in Masonry and the Shrine and is the Grand Royal Arch Captain of the Grand Chapter of Royal Arch Masonry of Michigan.

Dr. and Benta Hudson were married June 17, 1920 and have two sons, both married: William Andrew Hudson, Jr. and his wife Margaret, who live in Oklahoma City; and John Wallace Hudson and his wife Barbara and their two children William and Frances, who live on the Old Hudson Homestead near Jasper, Arkansas known as "Hudsonakers".

Third International Congress on Diseases of the Chest

BARCELONA, SPAIN, OCTOBER 4 - 8, 1954

The Third International Congress on Diseases of the Chest sponsored by the Council on International Affairs of the American College of Chest Physicians and presented under the Patronage of the Spanish Government, will be held in Barcelona, Spain, October 4 through 8, 1954. We are pleased to present on the following pages the preliminary scientific program for the Congress, prepared under the chairmanship of Dr. Andrew L. Banyai, Milwaukee, Wisconsin. More than two hundred scientific papers covering all aspects of heart and lung disease will be presented by speakers from forty-one countries throughout the world.

In addition to the following formal presentations there will be panel discussions and motion picture sessions on diseases of the chest. The final program is being prepared in Barcelona with summaries translated into the four official languages of the Congress, i.e., Spanish, French, German and English.

His Excellency Francisco Franco is serving as the Honorary President of the Congress and other officers are Dr. Luis Rosal, President, Dr. Cristobal Martinez, the Marquis de Villaverde, Vice-President, and Dr. Anthony Caralps, Secretary General. It is most important that everyone planning to attend the Congress is registered at the office of the Secretary General, Dr. Caralps, *Corcega 393, Barcelona, Spain*, in order that each participant will receive, upon arrival in Barcelona, his official documents and invitations to the scientific sessions and social functions. It is therefore requested that those members who have not yet registered with Dr. Caralps, please do so at once, *by air mail*.

PRELIMINARY PROGRAM

TUESDAY, OCTOBER 5, 1954 — HALL A

Carcinoma and Other Tumors

"Uncommon Intrathoracic Tumors," Anthony Caralps Masso, Barcelona, Spain

"The Frequency of Tumors of the Respiratory System," Giovanni L'Eltore, Rome, Italy

"The Early Diagnosis of Bronchial Carcinoma," H. W. Knipping, Koln-Lindenthal, Germany

"Pulmonary Carcinoma in Printing Workers," Erik Ask-Upmark, Upsala, Sweden

"Diagnostic and Therapeutic Results in 1,000 Cases of Bronchogenic Carcinoma," J. Swierenga, Utrecht, Netherlands

"Diagnosis and Differential Diagnosis of Tuberculosis and Carcinoma by Pleuroscopy," Anton Sattler, Vienna, Austria

"Bronchial Adenomas," G. Manresa Formosa, Barcelona, Spain

"Tumors of the Thymus," Roger Touraine, Lyon, France

"Results of Surgical Treatment of Cancer of the Esophagus," J. C. Rudler, Paris, France

Hydatid Disease

"Hydatid Cyst of the Lung, Surgical Treatment of 150 Cases," Jorge Alberto Taiana, Buenos Aires, Argentina

"Hydatid Disease of the Lung," Sinasi Guchan, Istanbul, Turkey

So-Called Hypertrophic Emphysema

"Pathogenesis and Treatment of So-Called Hypertrophic Emphysema," Andrew L. Banyai, Milwaukee, Wisconsin, U.S.A.

"Pulmonary Ventilation and Circulation in Chronic Pulmonary Emphysema of the Lung," Karl Vuylsteek, Ghent, Belgium

"Emphysema in the Tuberculosis Clinic," O. Garcia Rosell, Lima, Peru

Cystic Disease of the Lung

"Anatomical Aspects of Congenital Cysts of the Lung," Jose Reventos, Barcelona, Spain

"Air Cysts of the Lung," Nicola Sanguigno, Palermo, Italy

"Vanishing Lung," H. Wamsteker, Bloemendaal, Netherlands

Miscellaneous Subjects

"Oil Granuloma of Lung (Lipoid Pneumonia)," M. P. Susman, Sydney, Australia

"Simultaneous Bilateral Spontaneous Pneumothorax," Jose Turell Guma, Barcelona, Spain

TUESDAY, OCTOBER 5, 1954 — HALL B

Cardiovascular Diseases

"The Surgical Aspects of Patent Ductus Arteriosus," George Mason, Newcastle-upon-Tyne, England

"Bronchiectasis," Nicolaas G. M. Orie, Groningen, Netherlands

"Physiopathology of Mitral Stenosis," I. Balaguer-Vintro, Barcelona, Spain

"Surgical Treatment of Congenital and Acquired Heart Diseases," Decio Ferreira, Lisbon, Portugal

"Ligation of the Inferior Vena Cava Prior to Commissurotomy," Rodolfo Redi, Bari, Italy

"The Status of Cardiovascular Surgery in Cuba," Antonio Rodriguez Diaz, Havana, Cuba

"Surgical Treatment of Inter-auricular Septal Defects," Jose Paravisini Parra, Barcelona, Spain

"Massive Occlusive Auricular Thrombosis After Mitral Commissurotomy and the Prophylactic Administration of Anticoagulants Following Cardiac Surgery," A. P. Naef, Lausanne, Switzerland

"Comparison Between the Primary Results, Late Results and Complications of Valvulotomy for Mitral Stenosis," Helge B. Wulff, Malmo, Sweden

"Surgical Results of Mitral Commissurotomy," Isidro Perianes, Buenos Aires, Argentina

Tomography

"Pulmonary Tomography, Experimental and Clinical Results," Guido Pollitzer, Buenos Aires, Argentina

"Tomography of the Respiratory Tract," Andres Pursell Menguez, Barcelona, Spain

"Auxiliary Tomography with Photo-Roentgenology," Alvaro Urgoiti, La Coruna, Spain

Cytology

"Clinical and Cytologic Aspects of Pulmonary Enzymatic Therapy," Seymour M. Farber, San Francisco, California, U.S.A.

"Cytological Patterns in Broncho-Pulmonary Disease," A. A. Carabelli, Trenton, New Jersey, U.S.A.

"Systematic Chemical and Cytological Study of Intrathoracic Fluids," Ricardo Vidal-Ribas, Barcelona, Spain

TUESDAY, OCTOBER 5, 1954 — HALL B (Continued)

Industrial Dust Diseases

"The Role of Non-Industrial Silicosis in Tuberculosis of the Bronchial Lymph Nodes in the Aged," Hans Wurm, Wiesbaden, Germany

"Animal Experimental Basis of Research in Pneumoniosis," K. W. Joetten, Munster in Westfalen, Germany

"On a Special Kind of Pneumoconiosis," Lopo de Carvalho Cancella, Parede, Portugal

Miscellaneous Subjects

"Our Experience with Resection in Non-Tuberculous Diseases of the Lung," J. Juncosa, Barcelona, Spain

"Surgery of the Diaphragm," David H. Waterman, Knoxville, Tennessee, U.S.A.

"The Value of Elective Angiopneumography in the Study of Bullous Cavities," Antonio Leal Batoreo, Lisbon, Portugal

TUESDAY, OCTOBER 5, 1954 — HALL C

Tuberculosis

"Origin of the Koch Bacillus," Conrad Xalabarder Puig, Barcelona, Spain

"The Problems of Bacterial Resistance in Antimicrobial Therapy of Tuberculosis," Henry C. Sweany, Tampa, Florida, U.S.A.

"The Study of Tumor-like Formations in Pulmonary Tuberculosis," Jacques Stephani, Montana, Switzerland

"Anatomico-Clinical Forms of Regressive Phases of Tracheobronchial Tuberculosis and Its Treatment," Luis Saye, Barcelona, Spain

"Tuberculous Bronchopneumonia," A. Orti Alcantara, Barcelona, Spain

"What is the Value of Therapeutic Pneumothorax?," Eduard Arnold, Leysin, Switzerland

"Ambulatory Pneumoperitoneum on Chinese," Richard Eng, Hong Kong, China

"Prothesis with Lucite Balls in a Nylon Enclosure," Henry Joly, Haute-Savoie, France

"Pulmonary Resection for Tuberculosis; A Review of 300 Cases," Mariano Lopez Belio, Chicago, Illinois, U.S.A.

"The Place of Monaldi Drainage in the Treatment of Cavitary Pulmonary Tuberculosis," W. Jullien, Pau, France

"Segmental Resection for Tuberculosis (Experience with 500 Cases)," J. Maxwell Chamberlain, New York, New York, U.S.A.

"The Necessity of Early Surgical Therapy in Pulmonary Tuberculosis," Nunzio Di Paola, Rome, Italy

"The Anti-Inflammatory Non-Specific Treatment in Combination with Specific Drugs in the Treatment of Pulmonary Tuberculosis," Geraro Favez, Lausanne, Switzerland

"The Association of Chemotherapy and Immunization in Chronic Pulmonary Tuberculosis," Giusto Fegiz, Rome, Italy

"The Role of the Sanatorium in the New Treatment of Tuberculosis," Maurice Gilbert, Geneva, Switzerland

"The Activity of Substituted Thioureas in Experimental Tuberculosis in Mice and Guinea Pigs," R. L. Mayer, Summit, New Jersey, U.S.A.

"Rehabilitation in Tuberculosis," John H. Aides, Los Angeles, California, U.S.A.

"PAS, Drop by Drop, Intravenous," Manuel Albertal, Buenos Aires, Argentina

"A Twenty Year Follow-Up on Cases of Minimal Pulmonary Tuberculosis," Charles E. Hamilton, Brooklyn, New York, U.S.A.

WEDNESDAY, OCTOBER 6, 1954 — HALL A

Cardiovascular Diseases

"The Electrocardiogram in Mitral Stenosis Before and After Commissurotomy," John Gibert-Queralto, Barcelona, Spain

"A Clinical Evaluation of the Comparative Results Obtained in Mitral, Aortic, and Combined Commissurotomy," William Likoff, Philadelphia, Pennsylvania, U.S.A.

"Surgery of the Heart," I. Boerema, Amsterdam, Netherlands

"Packing in Giant Aortic Aneurysms," Armando Alonso Vial, Santiago, Chile

"Surgical Treatment of Coarctation of the Aorta," Enrique Garcia-Ortiz, Madrid, Spain

"A Case of Double Wound of the Heart," Antonio Ramirez, Medellin, Colombia

"Injuries of the Heart and Mediastinum," A. R. Valle, Detroit, Michigan, U.S.A.

"The Permanent Digitalization of Patients with Chronic Heart Disease," Walter Unverricht, Berlin, Germany

"Tuberculosis Pericarditis," P. K. Ghosh, Calcutta, India

Bronchography

"Study of Various Contrast Media in Bronchography," E. Concina, Torino, Italy

"Bronchography in Children," Carlo Gatti Manacini, Brescia, Italy

"Value of Bronchography in Determining the Indication for Pulmonary Decortication," Luigi Pigorini, Rome, Italy

Miscellaneous Subjects

"Regressive Giant Bullous Emphysema in the Adult," Donato G. Alarcon, Mexico D. F., Mexico

"Segmental and Diffuse Bronchitis," Francisco Tello Valdivieso, Zaragoza, Spain

"X-ray Finding of Pulmonary Paragonimiasis," Sze-Piao Yang, Taipei, Formosa

"The Syndrome of Alveolar-Capillary Block of Unknown Origin," J. G. Roosenburg, Utrecht, Netherlands

"Acute Respiratory Changes in Influenza of Infants," Bernardo Perez Moreno, Valladolid, Spain

"Pulmonary Brucellosis," Alvis E. Greer, Houston, Texas, U.S.A.

WEDNESDAY, OCTOBER 6, 1954 — HALL B

Carcinoma and Other Tumors

"The Use of the Horizontal Tomograms in the Determination of Operability in Pulmonary Carcinoma," E. Forster, Strasbourg, Germany

"Research on Pulmonary Neoplasm," David Cooper, Philadelphia, Pennsylvania, U.S.A.

"Cancer of the Lung and Schistosomiasis," A. A. Silvany, Bahia, Brazil

"Bronchogenic Carcinoma—Clinico-Pathologic Aspects of 175 Necropsies," I. M. Reingold, Long Beach, California, U.S.A.

"Transparietal Aspiration Biopsy in the Diagnosis of Peripheral Tumors of the Lung," Andre Cazenave, Pau, France

"The Nature and Treatment of Bronchial Adenoma (Based on 79 Cases)," Coleman B. Rabin, New York, New York, U.S.A.

"Tumor and Tuberculosis in the Lung," Gunnar Berg, Oldesloe, Germany

"On the Relationship Between Pulmonary Tumors and Tuberculous Lymphadenogenous Perforation Scars of the Bronchial Wall," Ph. Schwartz, Warren, Pennsylvania, U.S.A.

WEDNESDAY, OCTOBER 6, 1954 — HALL B (Continued)

"Limitations of the Operability of Cancer of the Lung,"
Pierre Decker, Lausanne, Switzerland

"Posterior Mediastinal Malignant Tumor,"
Thomas L. Dwyer, Mexico, Missouri, U.S.A.

"Bronchial Adenoma," Andre Meyer, Paris, France

"Cancer of the Lung Five Years After Radiation Therapy,"
Juan Castillo, Havana, Cuba

Hydatid Disease

"Hydatid Cyst, Differential Diagnosis (Case Report),"
Ramon Reventos Reventos, Barcelona, Spain

"Surgical Management of Pulmonary Hydatid Diseases,"
Papken S. Mugrditchian, Beirut, Lebanon

Bronchopulmonary Suppuration

"Drainage Suction in Lung Abscess," Vincenzo Monaldi, Naples, Italy

"Surgical Treatment of Lung Abscess," A. Agusti, Barcelona, Spain

Bronchiectasis

"Bronchiectasis; Diagnosis and Treatment," M. Gili, Barcelona, Spain

"Bronchography in Children," Manuel Canizares, Quezon City, Philippine Islands

"The Prognosis of Bronchiectasis," A. M. Olsen, Rochester, Minnesota, U.S.A.

"The Surgical Treatment of Bronchiectasis; Statistical Results of 100 Cases,"
Marcel Berard, Lyon, France

Arteriovenous Aneurysm

"Arteriovenous Aneurysm of the Pulmonary Vessels With Special Reference to the Importance of Oxymetry During Operation,"
L. D. Eerland, Groningen, Netherlands

"Bilateral Arteriovenous Aneurysm of the Lung,"
Dominique Raton, Besancon, France

WEDNESDAY, OCTOBER 6, 1954 — HALL C

Diagnosis

"Pulmonary Changes in Septic Diseases," K. Bingold, Munchen, Germany

"Anatomical Basis of Hemoptysis," Jacinto Reventos Bordoy, Barcelona, Spain

Prophylaxis and Treatment

"Diagnosis, Prophylaxis and Treatment of Pulmonary Embolism,"
Antonio Rodriguez Arias, Barcelona, Spain

"Aerosol Therapy of Chronic Non-Specific Infections of the Tracheo-Bronchial Tract," Jose Pablo Garcia Echevarria, Bilbao, Spain

"The Management of Esophageal Varices in Cirrhosis of the Liver in the Absence of Gastrointestinal Hemorrhage," Irving B. Brick, Washington, D. C., U.S.A.

Tuberculosis

"The Relationship Between Tonsillar Pathology and Pulmonary Ganglia,"
Egidio Lenci, Rome, Italy

"The Role of Pneumothorax in the Treatment of Tuberculosis,"
Fernand E. Cardis, Lausanne, Switzerland

"Wider Indications of Pneumolysis,"
Harald Malluche, Falkenstein im Taunus, Germany

WEDNESDAY, OCTOBER 6, 1954 — HALL C (Continued)

"Pneumoperitoneum—Indications and Results," Juan Aguilera Mas, Barcelona, Spain

"Thoracoplasty with Insufflation," Fernando Marques, Lisbon, Portugal

"Residual Cavities After Thoracoplasty: A Therapeutic Study," L. Luengo Serrano, Barcelona, Spain

"The Morelli-Di Paola Thoracoplasty in the Surgical Treatment of Pulmonary Tuberculosis," Paul Kyrle, Vienna, Austria

"Place of Thoracoplasty in Combination with Pulmonary Resection," Alfred F. Brunner, Zurich, Switzerland

"Indications and Limitations of Surgical Treatment of Bilateral Pulmonary Tuberculosis," Azio Valli, Forli, Italy

"Segmental Resection in Pulmonary Tuberculosis. A Critical Study of Our First 100 Cases," A. Marmet, Colmar, France

"Surgical Collapse Therapy in Tuberculous North African Mohammedans," A. Levi-Valensi, Algiers, Algeria

"Re-Resections for Complications After Resection Therapy for Pulmonary Tuberculosis," Jan K. Kraan, Appelscha, Netherlands

"Late Results with Extraperiosteal Pneumolysis with Polystan," Diego Garcia Alonso, Santander, Spain

"Gas-Analytical and Broncho-Spirometrical Examinations of the Blood in Connection with Lung Surgery," Joachim Hein, Schleswig-Holstein, Germany

"Resection in Pulmonary Tuberculosis," Alfred D. Dumont, Brussels, Belgium

"Early Pulmonary Resection for Tuberculosis," Rui de Lima, Lisbon, Portugal

"Miliary Tuberculosis Complicating Pregnancy," Maurice D. Kenler, New Bedford, Massachusetts, U.S.A.

"Inhibitory Effect of Tuberculous Pathologic Material Upon Isonicotinic Acid Hydrazide," M. Morellini, Rome, Italy.

"The Use of Streptomycin, Isoniazide and PAS in Treatment of Advanced Pulmonary Tuberculosis," Carlos Maldonado, Puerto Montt, Chile

THURSDAY, OCTOBER 7, 1954 — HALL A

Bronchial Asthma

"Histological Studies of Aspirated Bronchial Secretions in Bronchial Asthma," Raimundo Frouchtman Rager, Barcelona, Spain

"Cardiovascular Origin of Asthma and the Treatment of Asthmatic Dyspnea," Lino Businco, Rome, Italy

"Pathogenesis and Etiology of Bronchial Asthma," Santiago Millanes Marcos, Logrono, Spain

"Bronchial Asthma: Etiology and Causal Therapy, Results of Respiratory Alteration," Walter Roloff, Leipzig, Germany

"Bacteriology of Aspirated Bronchial Secretions in Bronchial Asthma," Roberto Foz, Barcelona, Spain

"The Study and Treatment of the Asthmatic Patient," Harry L. Rogers, Philadelphia, Pennsylvania, U.S.A.

"Characteristics of Asthma in the Canary Islands," Camilo Rodriguez Cavilanes, Las Palmas, Spain

"Treatment of Bronchial Asthma with Intravenous Novocain and Respiratory Exercises," R. A. Faris, Amman, Jordan

"BCG Treatment in Asthma," Jose Oriol Anguera, Barcelona, Spain

"The Prevention and Control of Bronchial Asthma by Continuous Postural Drainage," L. Bedford Elwell, Brisbane, Queensland, Australia

THURSDAY, OCTOBER 7, 1954 — HALL A (Continued)

"Bacterial Vaccine Therapy in Bronchial Asthma,"
Julian Lazaro Romeo, Bilbao, Spain

"The Treatment of Asthma," Louis Leopold Denis, Brussels, Belgium

Surgery of the Thoracic Duct and Bronchi

"The Cannulization of the Thoracic Duct in Humans: A Radiological and Physiological Study," Alfred Goldman, Beverly Hills, California, U.S.A.

"Plastic Tracheal and Bronchial Anastomosis,"
Eduardo Esteves Pinto, Porto, Portugal

"Intrathoracic Rupture of the Trachea and Major Bronchi,"
John V. Thompson, Indianapolis, Indiana, U.S.A.

"Closure of the Bronchus in Pulmonary Resections,"
M. C. A. Klinkenbergh, Utrecht, Netherlands

Diagnosis

"Mediastinography with Pneumomediastinum,"
Maurice Jacques Bariety, Paris, France

"Displacement of Heart and Large Vessels in Chronic Pulmonary Disease,"
Wladdimir Griffel, Preston, England

"Diagnostic Interpretation of Basal Pulmonary Shadows,"
Jose Cornudella, Barcelona, Spain

"Rheumatoid Syndrome in Intrathoracic Lesions: Vagal Reflex or Not?,"
Jans L. Hansen, Copenhagen, Denmark

THURSDAY, OCTOBER 7, 1954 — HALL B

Tuberculosis

"Migratory Pulmonary Infiltration with Eosinophilia of the Blood,"
Wilhelm Loeffler, Zurich, Switzerland

"Anatomico-Clinical Studies of Bronchial Tuberculosis in Pulmonary Resection,"
Juan Bta. Roset Coll, Barcelona, Spain

"Status of the Anti-Tuberculosis Campaign in the Philippines,"
Manuel Quisumbing, Sr., San Pablo City, Philippine Islands

"Present Status of Collapse Therapy in Pulmonary Tuberculosis,"
Benjamin P. Potter, Weehawken, New Jersey, U.S.A.

"Our Experience with 110 Cases of Extrapleural Pneumonolysis,"
Fernando Ma. Mugica Iza, Bilbao, Spain

"Intrapleural and Extrapleural Pneumolysis,"
Rlias Abdallah Sader, Beirut, Lebanon

"The Pathogenesis and the Surgical Treatment of Pulmonary Tuberculosis,"
Shinobu Miyamoto, Tokyo, Japan

"The Association of Intercavitary Aspiration and of Surgical Pneumothorax in the Treatment of Otherwise Desperate Cases,"
Maurizio Mendes, Jerusalem, Israel

"Critics on Monaldi Cavity Drainage and Maurer Tamponade in the Local Treatment of Tuberculosis Cavities," Ihsan Rifat Saber, Istanbul, Turkey

"Research on the Combined Use of Streptomycin and Isoniazid,"
L. Checcacci, Pavia, Italy

"Collective Critical Review of Current Therapy in Pulmonary Tuberculosis: A Study of 100 Participating Physicians with Analysis of Their Opinion,"
Harold G. Trimble, Oakland, California, U.S.A.

"Streptomycin and Isonicotinic Hydrazide in Pulmonary Tuberculosis,"
A. Omodei Zorini, Rome, Italy

THURSDAY, OCTOBER 7, 1954 — HALL B (Continued)

"Anatomical Modifications of Tuberculous Lesions Treated with Chemotherapy," J. F. Valiente, San Salvador, El Salvador

"Intrabronchial Local Application of Antibiotics in the Management of Inert Pulmonary Cavities Treated with Collapse Therapy," Bruno Besta, Rome, Italy

"Treatment of Fibrocaseous Lesions with Antibiotics, Tuberculin and Iodides," Euro Torres Leon, Guayaquil, Ecuador

"Clinical Observations of the Antituberculous Activity of Diphenyl Thiourea Compounds," Joseph A. Schwartz, San Fernando, California, U.S.A.

"Active and Prophylactic Management of Tuberculosis in Pregnancy," Irving Selikoff, Paterson, New Jersey, U.S.A.

"Pulmonary Vascular Changes in Patients Treated with Antibiotics and Chemotherapy," Carlo Pana, Rome, Italy

"The Changing Tuberculosis Control Program in the United States," R. J. Anderson, Washington, D. C., U.S.A.

"A Study of Factors Involved in Reactivation of Pulmonary Tuberculosis Over a Five Year Period Among Patients Discharged from Sanatoria as Arrested," Oscar Feinsilver, Worcester, Massachusetts, U.S.A.

"Post-Sanatorium Management for Tuberculous," Donald McKay, Buffalo, New York, U.S.A.

"Comparative Study of a Dried and a Wet BCG Vaccine," Toshieki Ebina, Sendai, Japan

"The Experimental Comparison Regarding Development of Tuberculosis Infection with Normal Bacteria as Compared to Streptomycin Resistant Bacteria," S. Gunella, Parma, Italy

THURSDAY, OCTOBER 7, 1954 — HALL C

Cardiovascular Diseases

"Hydatid Cysts of the Heart," Pablo Purriel, Montevideo, Uruguay

"Optimism in Heart Disease," John F. Briggs, St. Paul, Minnesota, U.S.A.

"Neuro-Hormonal Factors in Cardiac Pathology," Wilhelm Raab, Burlington, Vermont, U.S.A.

"Rehabilitation in Coronary Artery Occlusion," R. W. Kissane, Columbus, Ohio, U.S.A.

"Dextrocardia and Situs Inversus," Emil Bogen, Olive View, California, U.S.A.

"Correlation Between Right Ventricular Hypertrophy and Direct Intracardiac Pressure," M. Torner-Soler, Barcelona, Spain

"Further Studies With External Electrical Stimulation for Verticular Standstill," Elmer C. Rigby, Los Angeles, California, U.S.A.

"Quinidine in Auricular Fibrillation," Samuel A. Weisman, Los Angeles, California, U.S.A.

Bronchostenosis

"On the Pathogenesis and Practical Importance of Bronchostenosis and Allied Chronic Abnormalities (Except in Tuberculosis and Tumor Cases)," Alf V. Westergren, Stockholm, Sweden

"Bronchial Stenosis Caused by Parahilar and Mediastinal Calcification," Mario Benvenuti, Rome, Italy

Empyema

"Possibilities and Limitations of the Surgical Treatment of Chronic Empyema," Giuseppe Zorzoli, Rome, Italy

"Surgical Treatment of Non-Tuberculous Empyema," L. Gonzales, Barcelona, Spain

"Decortication for the Treatment of Empyema," Felipe Margarit, Barcelona, Spain

THURSDAY, OCTOBER 7, 1954 — HALL C (Continued)

Foreign Bodies in the Lung

"The Diagnosis of Vegetal Foreign Bodies in the Lower Respiratory Tract," Raymond Rosedale, Canton, Ohio, U.S.A.

"Latent Endo-Bronchial Foreign Bodies," Jacinto Sanglas Casanovas, Barcelona, Spain

Miscellaneous Subjects

"Pulmonary Manifestations in Schistosomiasis," E. Martinez-Rivera, Hato Rey, Puerto Rico

"Transparietal Extension of Pleuromediastinal Granulomas," Paul J. L. Desaive, Liege, Belgium

"The Relation of Aetiology to Radiographic Appearance in Pneumonia," John Crofton, Edinburgh, Scotland

"Middle Lobe Syndrome," A. Castella Escabros, Barcelona, Spain

"Pulmonary Lesions in Schistosomiasis," Jose Silveira, Bahia, Brazil

"Fibrothorax—Study and Therapy," F. Gonzalez Soler, Barcelona, Spain

FRIDAY, OCTOBER 8, 1954 — HALL A

Tuberculosis

"The Value of a Method of Areosol Bronchial Lavage for Obtaining Positive Cultures in Patients with Negative Sputa and Gastric Washings," Eugenio Fernandez-Cerra, Hato Rey, Puerto Rico

"BCG Vaccination," Georges Georgakopoulos, Athens, Greece

"BCG Vaccination in Ceylon," George E. Ranawake, Colombo, Ceylon

"Pregnancy and Breast-Feeding in Cases of Tuberculosis," Erik Hedvall, Uppsala, Sweden

"Pregnancy and Tuberculosis," Hollis E. Johnson, Nashville, Tennessee, U.S.A.

"The Treatment of Pulmonary Tuberculosis," Guiseppe Di Maria, Rome, Italy

"Tuberculin and Chemotherapy in Pulmonary Tuberculosis," R. Y. Keers, Aberdeenshire, Scotland

"Diaphragm Exercise in the Prevention of Ventilatory Insufficiency," Gosta Birath, Gothenburg, Sweden

"Chemotherapy in Patients with Pulmonary Tuberculosis of Apparently Unfavorable Prognosis," Albert Reginster, Liege, Belgium

"Streptomycin-Hydrazid Aerosol-Mist in Pulmonary Tuberculosis," Ugo Paolantonio, L'Aguilla, Italy

"The Evolution of Tuberculosis in Chile," Hector Orrego Puelma, Santiago, Chile

"Streptomycin and Isoniazid Treatment of Miliary Tuberculosis of the Lung in Infants," Umberto Monaco, Rome, Italy

"Experience with Isoniazid in Pulmonary Tuberculosis—Public Health Viewpoint," Irving Willner, Newark, New Jersey, U.S.A.

"Paradoxical Results of Incomplete Pneumothorax," Rafael Serra Goday, Barcelona, Spain

"The Importance of Hilar Lymph Nodes in the Origin of Complications After Resection Surgery," Tomas Seix Miralta, Barcelona, Spain

"Indications for Surgery in Tuberculosis After Treatment with Antibiotics and Chemotherapy," P. G. Schmidt, Waldbreitbach, Germany

"Endobronchial Treatment of Blocked Cavities," Raimundo Cornudella Mir, Barcelona, Spain

"Evolution and Present Status of Chemotherapeutics Tamponade of Pulmonary Cavities," Gustave Maurer, Zurich, Switzerland

FRIDAY, OCTOBER 8, 1954 — HALL A (Continued)

"The Limitations of Surgery in Pulmonary Tuberculosis," Eugenio Morelli, Rome, Italy

"Tuberculosis Among Nurses," Jay Arthur Myers, Minneapolis, Minnesota, U.S.A.

FRIDAY, OCTOBER 8, 1954 — HALL B

Cardio-respiratory Function Studies

"Circulatory Function Studies Prior to Thoracic Surgery," Juan Vives Uno, Barcelona, Spain

"The Importance of Angio-Cardiography and Selective Angiopneumography in Surgery of the Heart and Lungs," J. Martins da Fonseca, Lisbon, Portugal

"Selective Angiography of Pulmonary Vessels as a Functional Test in Thoracic Surgery," Wilhelm Bolt, Cologne, Germany

"Comparative Value of Bronchospirometry and Angiopneumonography in the Functional Examination of Each Lung," Raul F. Vaccarezza, Buenos Aires, Argentina

"Importance of Pulmonary Function Tests for Operative Indications in Chest Surgery," Carl B. Semb, Oslo, Norway

"The Relationship of the Movements of the Diaphragm and Respiratory Function," Anton L. Maccagno, Rome, Italy

"Respiratory Function Tests in Thoracopulmonary Surgery," Josef Verna, Cordoba, Argentina

"The Effects of Exercise on the Heart and Lungs," Burgess L. Gordon, Philadelphia, Pennsylvania, U.S.A.

"Respiratory Function Studies in Granulomatous Diseases of the Lung with Miliary Type Involvement," Jean M. Verstraeten, Ghent, Belgium

"Ventilation of the Non-Collapsed Tuberculous Lung," Paul Sadoul, Nancy, France

"Oximetry and Carboximetry During Thoracic Operations and in Respiratory Functional Research," R. Brinkman, Groningen, Netherlands

Diagnosis

"Chest Disease in Institutions," Otto L. Bettag, Chicago, Illinois, U.S.A.

"The Value of Mass X-ray Surveys in Non-Tuberculous Diseases of the Chest," Manoel de Abreu, Rio de Janeiro, Brazil

"Agenesis of the Lung," Agustin Ameli-Sans, Barcelona, Spain

"Idiopathic Pulmonary Hemosiderosis," Bianco G. Mariana, Rome, Italy

"Bronchopulmonary Ossifications Identified on Surgical Intervention," Henri Louis Le Brigand, Paris, France

"The Extrathoracic Causes of Cough," Barney M. Kully, Los Angeles, California, U.S.A.

"Congenital Malformations," Francisco Perez Marrero, Las Palmas, Spain

"Anatomical Aspects of Pulmonary Atelectasis," Enrique Bieto Reiman, Barcelona, Spain

"Pneumoperitoneum in Combination with Pneumothorax in the Diagnosis of Thoraco-Abdominal Conditions," Attilio DeMartini, Genoa, Italy

FRIDAY, OCTOBER 8, 1954 — HALL C

Carcinoma and Other Tumors

"The Necessity of Using Every Possible Technique in the Exact Diagnosis of Cancer of the Bronchus," Andre Soulas, Paris, France

"Possibilities and Limitations of Bronchial Aspiration in the Diagnosis of Lung Tumors," Francisco Coll Colome, Barcelona, Spain

FRIDAY, OCTOBER 8, 1954 — HALL C (Continued)

"Incidence and Location of Tumors of the Respiratory Tract," Onofrio Ceino, Rome, Italy

"Hypertrophic Osteoarthropathy in Association with Bronchial Carcinoma," Thomas Semple, Glasgow, Scotland

"A Pleural Type of Primitive Lung Cancer," G. Babolini, Naples, Italy

"Prolonging Life in Pulmonary Cancer," Richard H. Overholt, Brookline, Massachusetts, U.S.A.

"Early Diagnosis of Cancer of the Lung—Clinical Aspects," Edgar Mayer, New York, New York, U.S.A.

"Early Diagnosis of Cancer of the Lung—Bronchoscopic Aspects," Arthur J. Cracovaner, New York, New York, U.S.A.

"Pulmonary Manifestations of Adenomatosis," Enrico Fasano, Bologna, Italy

"Neoplasms of the Esophagus," Isidro Triadu Castellis, Barcelona, Spain

"Benign Intrathoracic Tumors," B. G. Begin, Montreal, Quebec, Canada

"Bronchiogenic Carcinoma and Tuberculous Lymph Node Calcifications," Paul Galy, Lyon, France

Hydatid Disease

"Experimental Studies in Hydatid Disease of the Lung," Jose Abello, Madrid, Spain

"Surgical Treatment of Hydatid Cyst of the Lung," Emir Cesar Chehab, Beirut, Lebanon

"Status of the Surgical Treatment of Hydatid Cyst of the Lung," Tomas Lorenzo Fernandez, Barcelona, Spain

Bronchopulmonary Suppuration

"Clinical Aspects and Frequency of Bronchopulmonary Suppurations in Private Practice," Gumersindo Sayago, Cordoba, Argentina

"Endobronchial Treatment of Lung Abscess," Jose Palou Llaudet, Barcelona, Spain

Loeffler's Syndrome

"On the Relationship Between So-Called Transitory Pulmonary Infiltration and Primary Atypical Pneumonia," Shinnosuke Fujita, Tokyo, Japan

"Transient Pulmonary Infiltration," P. Baringo Alcolea, Barcelona, Spain

Sarcoidosis

"Mediastino-Pulmonary Localization of Besnier-Boeck-Schaumann Disease," Gennaro Costantini, Naples, Italy

"Clinical Aspects of Sarcoidosis of the Lung," Ludwig Heilmeyer, Freiburg, Germany

"The Diagnosis of Sarcoidosis," Hugh G. Whitehead, Baltimore, Maryland, U.S.A.

OTHER INTERNATIONAL CONGRESSES

XIII Conference, International Union Against Tuberculosis
Madrid, Spain, September 26 - October 2, 1954.

8th General Assembly, World Medical Association
Rome, Italy, September 26 - October 2, 1954.

Third Congress, International Bronchoesophagological Society
Lisbon, Portugal, October 10 - 13, 1954.

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CALENDAR OF EVENTS

NATIONAL AND INTERNATIONAL MEETINGS

Third International Congress on Diseases of the Chest
Council on International Affairs
American College of Chest Physicians
Barcelona, Spain, October 4-8, 1954.

Interim Session, American College of Chest Physicians
Delano Hotel, Miami Beach, Florida, November 28-29, 1954.

POSTGRADUATE COURSES

9th Annual Postgraduate Course on Diseases of the Chest
Hotel Knickerbocker, Chicago, Illinois, October 18-22, 1954.

Postgraduate Course on Diseases of the Chest
Bunts Institute, Cleveland, Ohio, October 27-28, 1954.

7th Annual Postgraduate Course on Diseases of the Chest
Hotel New Yorker, New York City, November 8-12, 1954.

8th Annual Postgraduate Course on Diseases of the Chest
Bellevue-Stratford Hotel, Philadelphia, Pennsylvania, Spring, 1955.

ANNOUNCEMENTS

A unique collection of medical arts by such renowned masters as Rembrandt, Goya, Daumier, Vesalius, Toulouse-Lautrec and others will be shown at medical colleges and hospitals across the country during a tour launched by Smith, Kline & French Laboratories of Philadelphia. The collection, entitled "Arts Medica," or The Healing Arts, is composed of 85 prints depicting the practice of medicine over the centuries and was assembled by the Philadelphia Museum of Art through the support of Smith, Kline & French.

Parke, Davis & Company has introduced a new tablet form anticoagulant for treatment of such conditions as thrombo-embolic disease, both real and threatened. The new drug, Indon, is effective orally and gives a more rapid onset of therapy for a shorter duration of action than "Dicumarol". Each Indon tablet is grooved, contains 50 mg. of phenylindandione (2-phenyl-1, 3-indandione) and comes in bottles of 100.

Levinthal Electronic Products, Inc. announce the new Morris Clinical Pacemaker which is designed to provide an output suitable for the control of heart beat in cases of cardiac standstill or conduction block. Ready for full operation within five seconds after being energized, the Clinical Pacemaker can be used simultaneously with an electrocardiograph without interference, has a minimum number of simple controls, and can be used externally with either electrocardiograph-type chest-strap electrodes or with hypodermic needles as electrodes, or, in open-chest cases, in direct contact with the ventricles.

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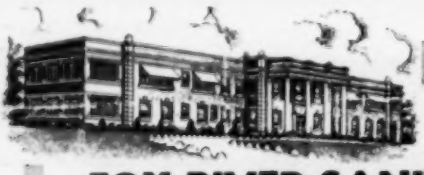

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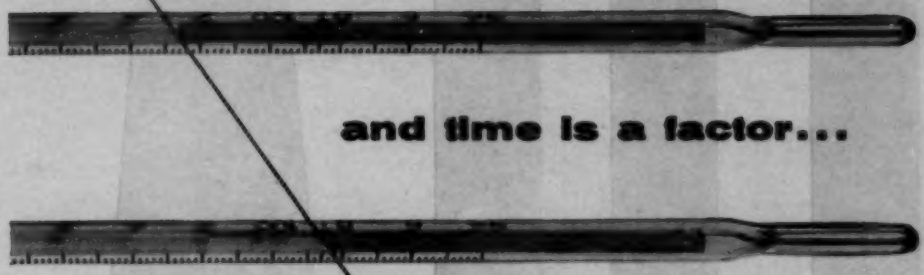

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Whenever you take a temperature, for a prompt response with outstanding toleration—consider Tetracyn in susceptible infections.

1. Filippis, H. F.: Philadelphia Med. 49:733 (Jan. 30) 1954.
2. Glatt, M., and Ross, S.: Antibiotics & Chemotherapy 4:395 (Apr.) 1954.

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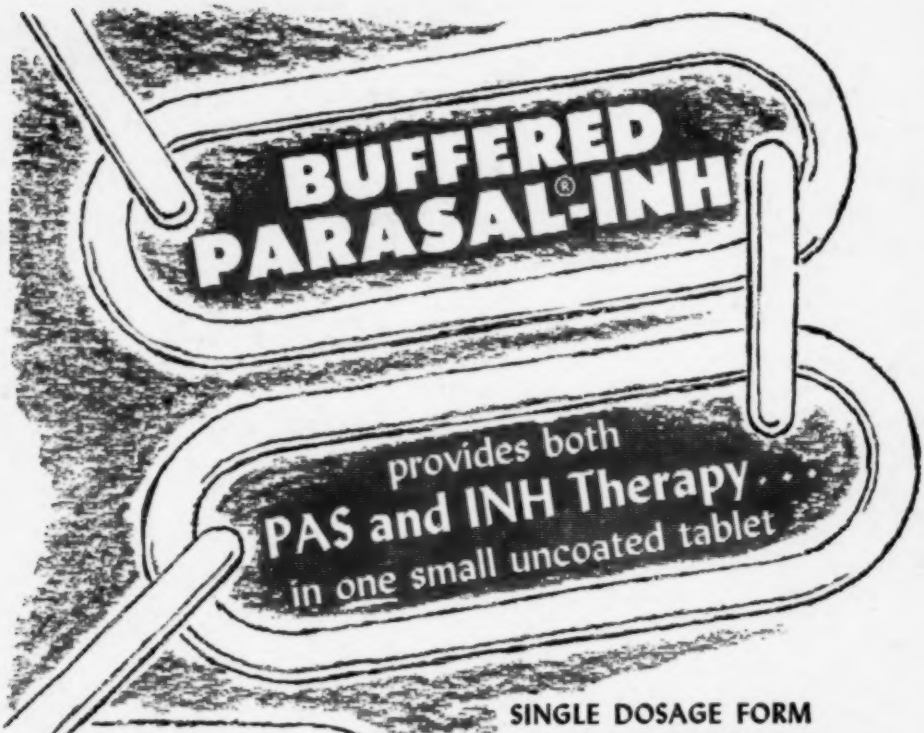

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